NEW DEVELOPMENTS IN THE 1-AZA-DIELS-ALDER REACTION – VERSATILE ROUTES TO PYRIDINES

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for the degree of Doctor of Philosophy

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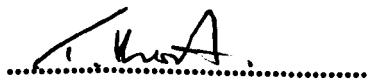
I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.



Abstract

In Chapter one a review of the 1-aza-Diels-Alder reaction is presented. The hetero-Diels-Alder reaction of 1-aza-1,3-butadienes with both alkene and alkyne dienophiles has been shown to be an efficient and versatile method for the preparation of a large range of nitrogen-containing six-membered heterocycles. The use of electron-rich 1-azadienes in the normal electron-demand Diels-Alder reaction is primarily examined, followed by a brief look at the synthetic applications of the inverse electron-demand process.

In Chapter two the intermolecular hetero-Diels-Alder cycloadditions of 3-siloxy-1-aza-1,3-butadienes with electron-deficient dienophiles is presented as an efficient route to tri- and tetra-substituted pyridine core of the thiopeptide antibiotic nosiheptide. A series of α,β-unsaturated oximes and hydrazones were prepared and subsequently shown to participate readily in the hetero-Diels-Alder reaction with dimethyl acetylenedicarboxylate.

In Chapter three, the intramolecular Diels-Alder reaction is presented as a versatile method for the preparation of chromeno[*c*]pyridines. First a series of model systems was prepared and shown to undergo thermally induced intramolecular cycloaddition. This methodology was then utilised in the rapid preparation of the penta-substituted pyridine core of the antitumour antibiotic streptonigrin.

Chapter four contains experimental procedures for all of the work detailed above.

Acknowledgments

First and foremost I would like to thank my supervisor, Professor Chris Moody for giving me the opportunity to work on such a challenging and interesting project, as well as for his constant support and patience over the past few years. I would also like to thank GlaxoSmithKline for providing funding and in particular to my industrial supervisor Dr. Tim Miles for his help and suggestions.

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Finally I would like to thank my parents, without whom I would not have had the opportunity to study for my PhD in the first place. Also, I would especially like to thank my girlfriend Liz for her constant love, support and understanding over the past several years.

Contents

Abbreviations

o-DCB	*ortho*-Dichlorobenzene
DCC	Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DIPEA	Diisopropylethylamine
DMAD	Dimethyl acetylenedicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DNA	Deoxyribosenucleic acid
HFIP	Hexafluoroisopropanol
HOMO	Highest Occupied Molecular Orbital
IMDA	Intramolecular Diels-Alder
LUMO	Lowest Unoccupied Molecular Orbital
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PFP	Pentafluorophenyl
PMB	*para*-Methoxybenzyl
RNA	Ribosenucleic acid
SOD	Superoxide Dismutase
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl

THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TMS	Trimethylsilyl

Chapter 1

Introduction

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The 1-Aza-Diels-Alder Reaction

1.1 Introduction to the 1-Aza-Diels-Alder Reaction

Since the pioneering work by Diels and Alder in 1928,[1] the Diels-Alder cycloaddition has become one of the most widely used and flexible methods for the synthesis of six-membered rings; reasons for this include the high degree of chemo-, regio- and diastereoselectivity observed with this reaction.

The Diels-Alder reaction itself may be classified into 3 different types based on the lowest energy gap between the frontier molecular orbitals involved in the transformation (**Figure 1**). The first type is the 'normal' electron-demand reaction which is controlled by the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile. The second type is the 'neutral' electron-demand reaction, where the $HOMO_{diene}$-$LUMO_{dienophile}$ and $HOMO_{dienophile}$-$LUMO_{diene}$ energy gaps are equivalent. The third type is the 'inverse' electron-demand Diels-Alder, and occurs where the lowest energy separation is between the LUMO of the diene and the HOMO of the dienophile.

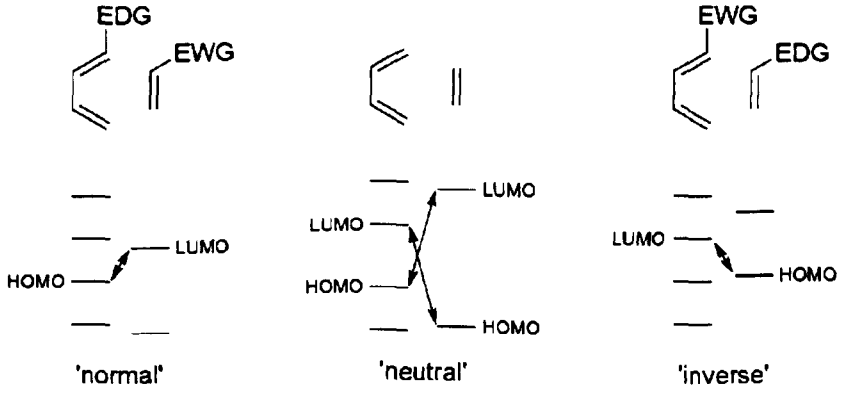


Figure 1.

The rate of cycloaddition may be increased by improving the interaction between the relevant molecular orbitals by reducing the energy gap between them. This may be achieved through the introduction of appropriate substituents onto the diene or dienophile, or by the use of appropriate catalysts. Thus, for a 'normal' demand Diels-Alder reaction addition of electron-donating substituents into the diene and electron-withdrawing groups into the dienophile serves to increase the reaction rate. Conversely, electron-withdrawing groups on the diene and electron-donating groups on the dienophile increase the rate in the 'inverse' demand reaction.

Diels-Alder methodology has been extended to the synthesis of heterocyclic compounds through substitution of one or more of the carbon atoms in either the diene or the dienophile with a combination of C, N, O or S atoms. In the synthesis of nitrogen-containing six-membered heterocycles, three complementary strategies have been developed, namely the 1-aza, 2-aza and imino-Diels-Alder reactions (**Figure 2**). In this discussion, the focus will be on the 1-aza-Diels-Alder reaction.

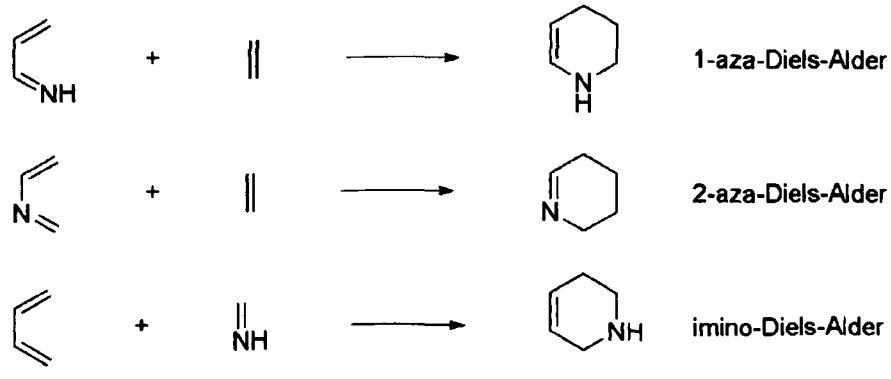
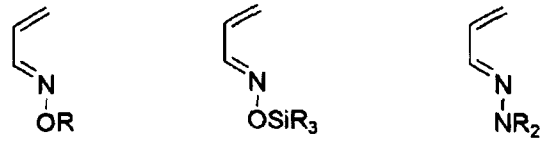


Figure 2.

Introduction of the electron-withdrawing nitrogen atom at the 1-position of the diene lowers its reactivity in the 'normal' demand Diels-Alder reaction with electron-deficient dienophiles, which has limited the synthetic potential of unactivated 1-azadienes. Exceptions to this include the use of *o*-quinone methide imines as dienes and certain intramolecular reactions. The use of *N*-alkyl-1-azadienes has been extended only in recent years through the introduction of appropriately activating substituents into the C-2, C-3 and C-4 positions of the diene. However, they shall not be considered further in this discussion.[2]

Incorporation of an electron-releasing substituent in the form of an alkoxy, siloxy or dialkylamino group at the *N*-terminus of the 1-azadiene furnishes a comparatively electron-rich system that is more reactive towards electron-poor dienophiles (**Figure 3**). For this reason, these systems, in particular the α,β-unsaturated *N,N*-dialkylhydrazones **3**, have received much attention in the literature for the synthesis of six-membered nitrogen heterocycles.[2-8]



1 **2** **3**

Figure 3. Examples of electron-rich 1-aza-1,3-butadienes

More recently, elegant work by Boger[9-15] and Fowler[16-21] has demonstrated the synthetic potential of the 'inverse' demand 1-aza-Diels-Alder reactions of various *N*-sulfonyl-1-aza-1,3-butadienes **4** and 2-cyano-1-azadienes **5** (**Figure 4**).

4 **5**

Figure 4.

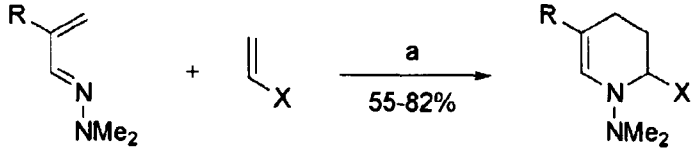
A representative evaluation of the inter- and intramolecular hetero-Diels-Alder reactions of electron-rich 1-aza-1,3-butadienes with alkene and alkyne dienophiles will be presented, followed by those of electron-deficient 1-aza-1,3-butadienes.

1.2 Hetero-Diels-Alder Reactions of Electron-Rich 1-Azadienes with Alkene Dienophiles

The hetero-Diels-Alder reaction of α,β-unsaturated *N*,*N*-dimethylhydrazones has been extensively employed in the synthesis of six-membered nitrogen-containing heterocycles.[2, 8] Pioneering work in this area was carried out by Léon Ghosez and coworkers, who first rationalised that the strongly electron-releasing nature of the dimethylamino substituent would enhance 1-azadiene reactivity towards electron-deficient dienophiles.[22]

The first 1-azadiene **7** used by Ghosez bears a simple methyl sustituent at C-3, and may be readily prepared by condensation of methacrolein with *N*,*N*-

dimethylhydrazine.[22] Introduction of this additional electron-releasing substituent into the C-3 position was found to be beneficial in the [4+2]-cycloaddition of 1-azabutadienes with electron-deficient dienophiles (**Scheme 1**). For example, treatment of methacrolein *N,N*-dimethylhydrazone **7** with acrylonitrile **8** or methyl acrylate **9** gave superior yields (**Table 1**, entries 3-4) compared to the acrolein derivative **6** (**Table 1**, entries 1-2).[23]



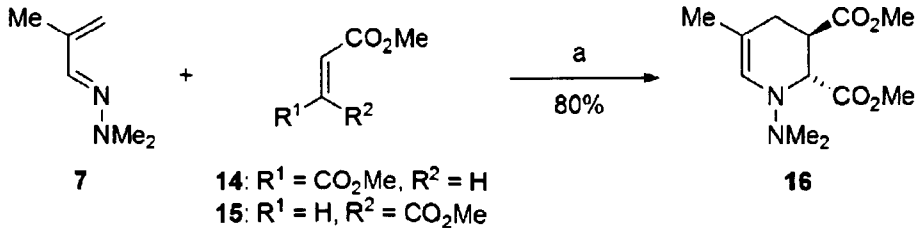
6-7 **8-9** **10-13**

Scheme 1. *Reagents and conditions*: a. benzene, 120 °C, sealed tube, 6-8 h.

Table 1. Diels-Alder reaction of hydrazones **6-7** with acrylonitrile **8** and methyl acrylate **9**.

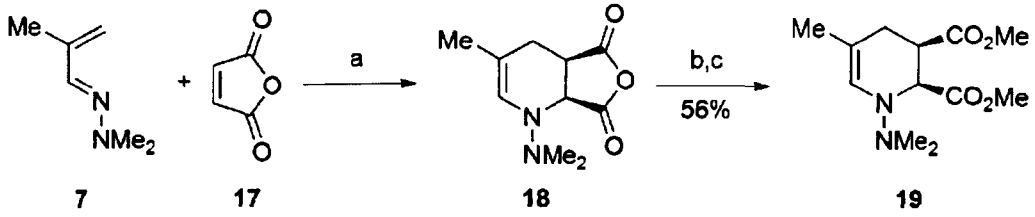
Entry	1-Azadiene	R	Dienophile	X	Product	Yield/%
1	**6**	H	**8**	CN	**10**	67
2	**6**	H	**9**	CO_2Me	**11**	55
3	**7**	Me	**8**	CN	**12**	82
4	**7**	Me	**9**	CO_2Me	**13**	70

Treatment of 1-azadiene **7** with dimethyl fumarate **14** (R^1 = CO_2Me, R^2 = H) or dimethyl maleate **15** (R^1 = H, R^2 = CO_2Me) afforded exclusively the *trans*-cycloadduct **16** (**Scheme 2**). The authors attributed this result to the isomerisation of dimethyl maleate **15** to the more stable *trans*-isomer prior to cycloaddition.[4, 22] Higher yields and lower reaction times have been obtained by carrying out the reaction under ultrasonic irradiation (50 °C, 49 h, 95-99%), although the *trans*-cycloadduct **16** was still the only observed product.[24]



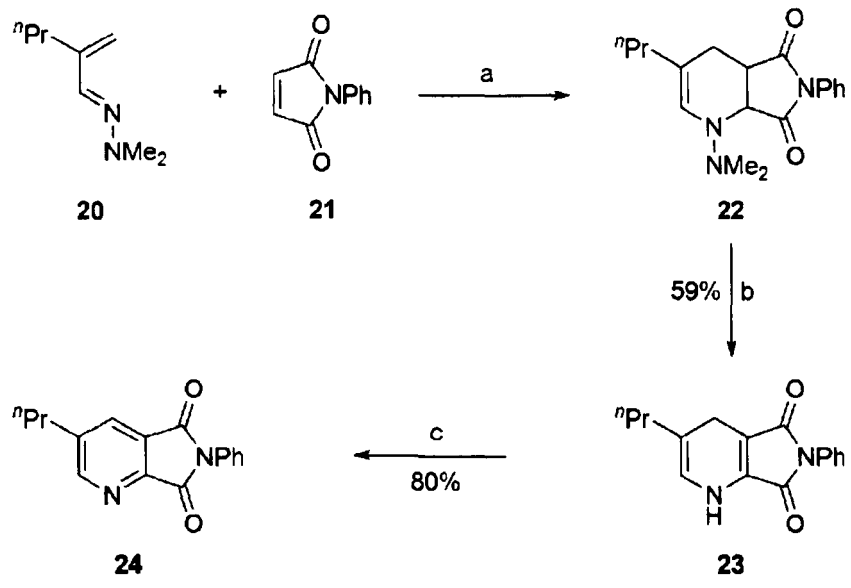
Scheme 2. *Reagents and conditions*: a. MeCN, reflux, 133-136 h.

In order to obtain the *cis*-cycloadduct **19**, maleic anhydride **17** was used as the dienophile under very mild conditions, followed by ring-opening and esterification with diazomethane (**Scheme 3**).[4, 22]



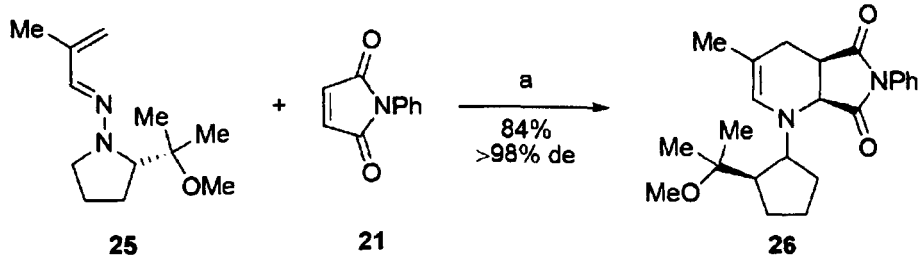
Scheme 3. *Reagents and conditions*: a. CH_2Cl_2, rt, 20 min; b. MeOH; c. CH_2N_2.

Treatment of the *n*-propyl analogue **20** with *N*-phenylmaleimide **21** generated the expected tetrahydropyridine **22**, which was then be converted to the dihydropyridine derivative **23** upon heating with silica gel in toluene. Oxidation to the pyridine **24** was achieved using MnO_2 in acetic acid (**Scheme 4**).[25]



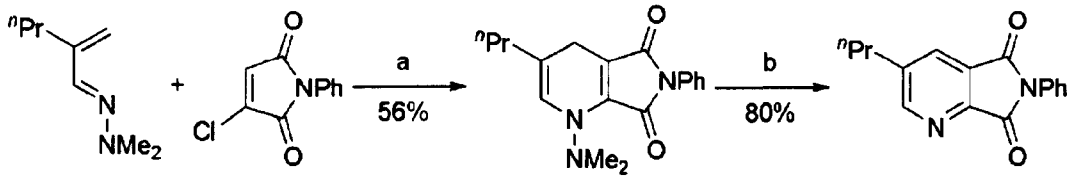
Scheme 4. *Reagents and conditions*: a. MeCN, 55 °C; b. SiO_2, toluene, reflux; c. MnO_2, AcOH, 60 °C.

An asymmetric variant of the hetero-Diels-Alder reaction was reported by Ghosez and coworkers. High degrees of diastereoselectivity were obtained for the cycloaddition between 1-azadiene **25**, derived from Enders' hydrazine, and various dienophiles including *N*-phenylmaleimide **21 (Scheme 5)**.[26]



Scheme 5. *Reagents and conditions*: a. MeCN, rt.

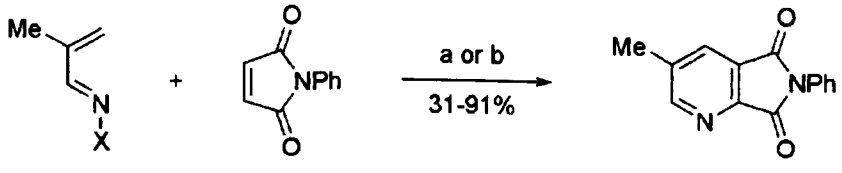
Waldner has shown that introduction of a halogen atom into the dieneophile allows direct formation of the dihydropyridine cycloadduct **28** via base induced elimination of hydrogen chloride. Aromatisation was then carried out with hydrochloric acid in dioxane (**Scheme 6**). 2-Chloroacrylonitrile was also successfully used as the dienophile.[27]



20 **27** **28** **24**

Scheme 6. *Reagents and conditions*: a. MeCN, Et_3N, 70 °C; b. HCl, dioxane, rt.

In 1991 Gilchrist and coworkers undertook a study designed to investigate the effect of different hydrazone substituents in hetero-Diels-Alder reactions (**Scheme 7**). Treatment of the *N*-benzoylhydrazone **29** with *N*-phenylmaleimide **21** afforded the desired pyridine **32** in good yield after elimination and formal oxidation (**Table 2**, entry 1). The *N*-tosyl and dinitrophenyl derivatives **30-31** performed less well (**Table 2**, entries 2-3), presumably because the stronger electron-withdrawing groups deactivate the diene too greatly for efficient cycloaddition to take place.[28, 29]



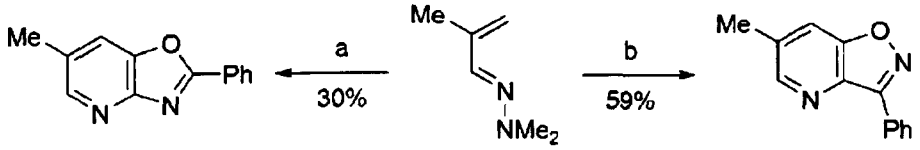
29-31 **21** **32**

Scheme 7. *Reagents and conditions*: a. xylene or mesitylene, reflux, 24-45 h.

Table 2. Effect of varying hydrazone substituents on 1-azadiene reactivity.

Entry	1-Azadiene	X	Product	Yield/%
1	**29**	NHCOPh	**32**	91
2	**30**	NHTs	**32**	31
3	**31**	$NHC_6H_3(NO_2)_2$	**32**	42

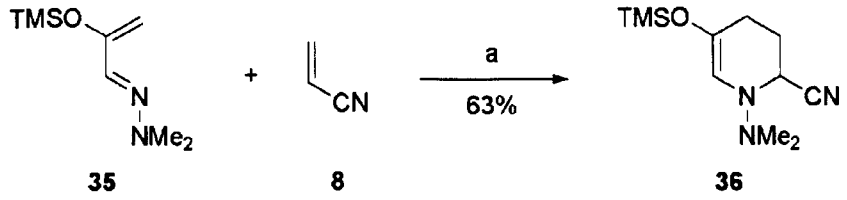
Oxazoles and isoxazoles may also participate as dienophiles in hetero-Diels-Alder cycloadditions when substituted with a suitable electron-withdrawing group, which also serves to control the regiochemistry (**Scheme 8**). Spontaneous loss of nitrous acid and dimethylamine afforded the pyridine derivatives **33** and **34**, without isolation of the primary cycloadducts.[30, 31]



33 **7** **34**

Scheme 8. *Reagents and conditions*: a. 4-nitro-2-phenyloxazole, $CHCl_3$, 55 °C, 48 h; b. 4-nitro-3-phenylisoxazole, $CHCl_3$, 55 °C, 48 h.

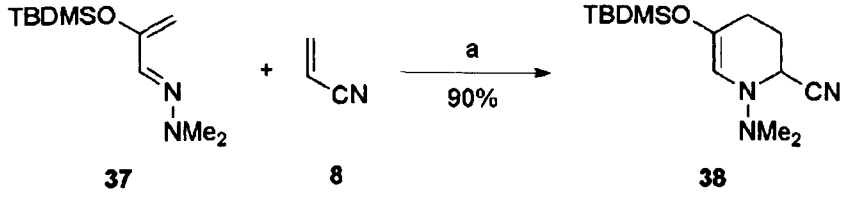
The 1-azadiene **35**, bearing a trimethylsiloxy group at C-3 was readily prepared from the mono(dimethyl)hydrazone of methylglyoxal on treatment with a slight excess of trimethylbromosilane. Addition of this electron-releasing group further increases the reactivity of the 1-aza-1,3-butadiene towards electron-deficient dienophiles, although the cycloadduct formed was relatively unstable and needed to be isolated under an inert atmosphere (**Scheme 9**).[23]



35 8 36

Scheme 9. *Reagents and conditions*: a. benzene, 110 °C, sealed tube, 2.5 h.

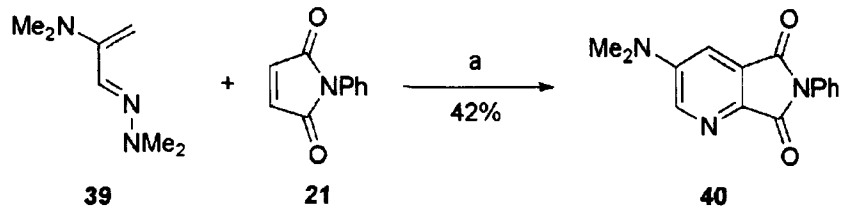
Ghosez and coworkers have also shown the benefit of introducing a siloxy group at the C-3 position of 1-azadienes. In this case the bulkier TBDMS group in 1-azadiene **37** (prepared in two steps from pyruvic aldehyde dimethylacetal by condensation with *N,N*-dimethylhydrazine followed by treatment with TBDMS triflate) proved more hydrolytically stable, allowing the tetrahydropyridine cycloadduct **38** to be isolated in excellent yield (**Scheme 10**). Dimethyl fumarate **14** and dimethyl maleate **15** were also shown to be efficient partners in [4+2]-cycloadditions with **37**.[4]



37 8 38

Scheme 10. *Reagents and conditions*: a. benzene, 100 °C.

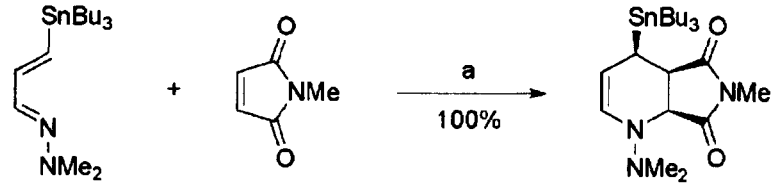
The presence of a dimethylamino group enhances the reactivity of 1-azadiene **39** to the extent that cycloaddition was almost instantaneous at room temperature, with concomitant loss of dimethylamine and oxidation to the substituted pyridine **40** (**Scheme 11**). A slower reaction and lower yield was observed with methyl acrylate **9**.[23]



39 21 40

Scheme 11. *Reagents and conditions*: a. Et_2O, rt, instantaneous.

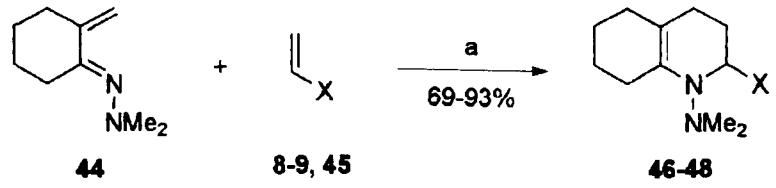
In 1997, Cuerva and coworkers reported the hetero-Diels-Alder reaction of tributylstannane **41** with *N*-methylmaleimide **42** in quantitative yield (**Scheme 12**). Quinonic dienophiles were also investigated.[32]



41 42 43

Scheme 12. *Reagents and conditions*: a. toluene, 70 °C, 48 h.

High reactivity in the 1-aza-Diels-Alder reaction may also be achieved by constraining the 1-azadiene into the favoured *s-cis* geometry. For example α-methylenecyclohexanone dimethylhydrazone **44** reacts in high yield with a range of dienophiles (**Scheme 13, Table 3**). Cyclic dienophiles including *N*-phenylmaleimide **21** and benzoquinone were also investigated.[23]



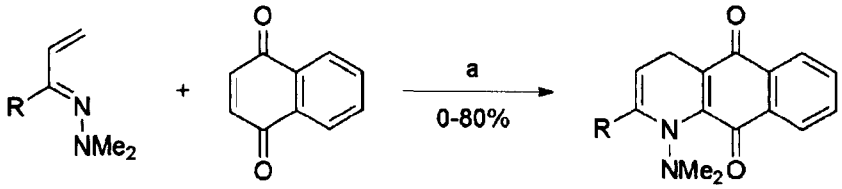
44 8-9, 45 46-48

Scheme 13. *Reagents and conditions*: a. benzene, 110 °C, 2 h.

Table 3. Diels-Alder reaction of hydrazone **44** with electron-poor dienophiles **8-9** and **45**.

Entry	Dienophile	X	Product	Yield/%
1	**8**	CN	**46**	93
2	**9**	CO_2Me	**47**	82
3	**45**	COMe	**48**	69

The introduction of a methyl group at the C-2 position of the 1-azadiene, however, lowers its reactivity in the hetero-Diels-Alder reaction (**Scheme 14**). For example, treatment of the unsubstituted diene **6** with naphthoquinone **50** afforded the cycloadduct **51** in good yield as assessed by ^1H nuclear magnetic resonance (NMR) analysis of the crude reaction mixture (**Table 4**, entry 1). The C-2 methylated analogue **49** on the other hand, failed to react under the same conditions (**Table 4**, entry 2).[4]



6, 49 **50** **51-52**

Scheme 14. *Reagents and conditions*: a. heat.

Table 4. Hetero-Diels-Alder reaction of hydrazones **6** and **49** with naphthoquinone **50**.

Entry	1-Azadiene	R	Product	Yield/%
1	**6**	H	**51**	80
2	**49**	Me	**52**	0

The authors attributed this effect to the increased steric hindrance between the methyl group at C-2 and the *N,N*-dimethylamino substituent (**Figure 5**). This pushes the nitrogen lone pair out of conjugation with the π-system, causing loss of activation of the diene, and hence lower reactivity.[4, 22]

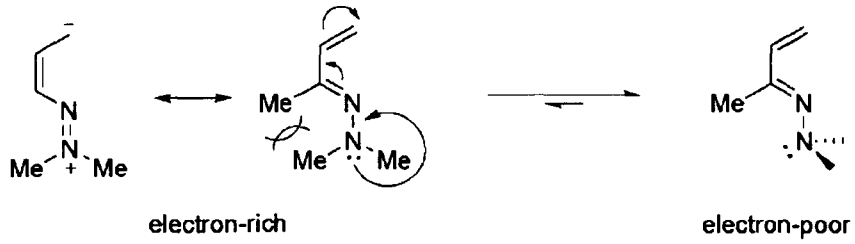
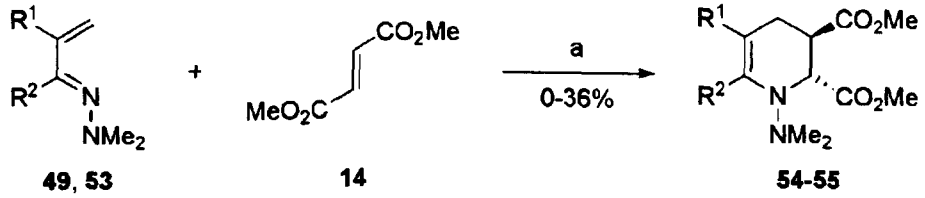


Figure 5. Deactivation of 1-aza-1,3-butadienes by C-2 substitution.

Strongly electron-releasing substituents such as a *tert*-butyldimethylsilyloxy group at C-3 compensate for this by increasing the electron density of the 1-azadiene, allowing cycloaddition to take place, albeit in modest yield (**Scheme 15, Table 5**).[4]

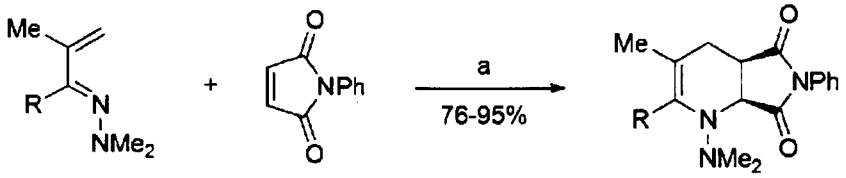


Scheme 15. *Reagents and conditions*: a. benzene, 100 °C, sealed tube.

Table 5. Hetero-Diels-Alder reaction of hydrazones **50** and **54** with dimethyl fumarate **14**.

Entry	1-Azadiene	R^1	R^2	Product	Yield/%
1	**49**	H	Me	**54**	0
2	**53**	OTBDMS	Me	**55**	36

Incorporation of an electron-withdrawing substituent into the C-2 position of the diene also lowers its reactivity, presumably through both steric and electronic interactions, as can be seen from the increased reaction times for 1-azadienes **56-57** with *N*-phenylmaleimide **21** versus diene **7** (**Scheme 16, Table 6**).[33]



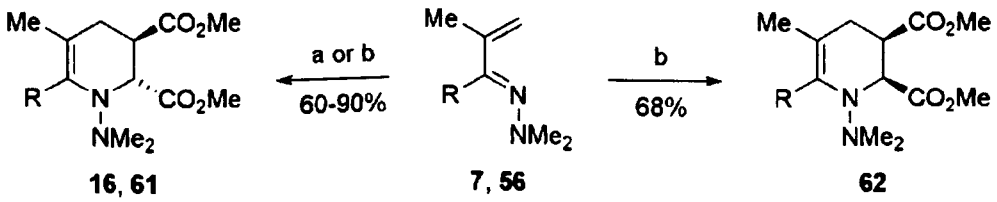
7, 56-57 **21** **58-60**

Scheme 16. *Reagents and conditions*: a. MeCN, rt.

Table 6. Hetero-Diels-Alder reaction of hydrazones **7** and **56-57** with *N*-phenylmaleimide **21**.

Entry	1-Azadiene	R	Time/d	Product	Yield/%
1	**7**	H	1	**58**	95
2	**56**	CN	14	**59**	91
3	**57**	CO_2Me	3	**60**	76

Stereospecific cycloaddition of 1-azadienes **7** and **56** with dimethyl fumarate **14** and dimethyl maleate **15** has also been achieved in the presence of lithium trifluoromethanesulfonimide as a Lewis acid catalyst, although reaction times are still relatively long (**Scheme 17, Table 7**).[33]



16, 61 **7, 56** **62**

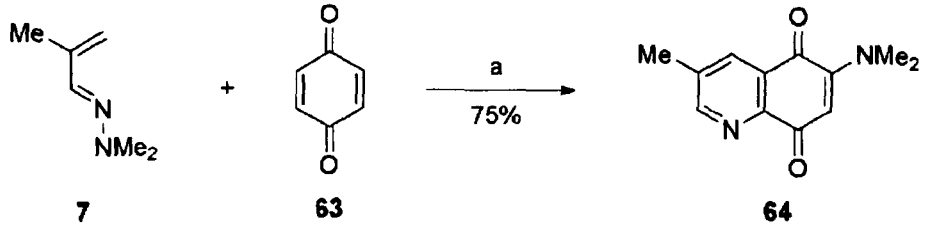
Scheme 17. *Reagents and conditions*: a. $LiNTf_2$, Et_2O, rt, 19 h; b. $LiNTf_2$, MeCN, 50 °C, 72 h.

Table 7. Hetero-Diels-Alder reaction of hydrazones **7** and **56** under Lewis acid catalysis.

Entry	1-Azadiene	R	Method	Dienophile	Product	Yield
1	**7**	H	a	**14**	**16**	90
2	**56**	CN	b	**14**	**61**	60
3	**56**	CN	b	**15**	**62**	68

Benzoquinone **63** and naphthoquinone **50** are both very reactive dienophiles, and form cycloadducts with a range of 1-azadienes.

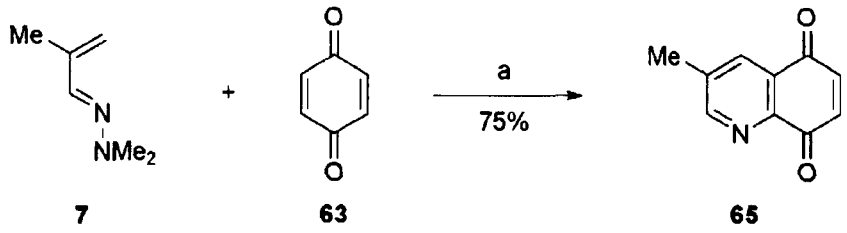
Treatment of Ghosez's diene **7** with benzoquinone **63** afforded the cycloadduct **64**, which arises from nucleophilic attack of the liberated dimethylamine at C-6 of the quinone (**Scheme 18**).[34] Similar results were obtained under ultrasonic irradiation.[24]



7 **63** **64**

Scheme 18. *Reagents and conditions*: a. benzene, rt.

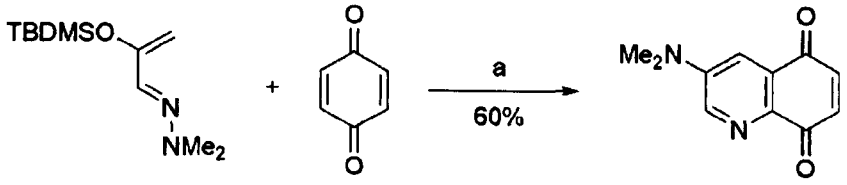
3-Methylquinoline-5,8-dione **65** may however be obtained in good yield by addition of a chloroformyl-polystyrene scavenger resin, which completely removes dimethylamine from the reaction mixture (**Scheme 19**).[35]



7 63 65

Scheme 19. *Reagents and conditions*: a. benzene, scavenger resin, rt

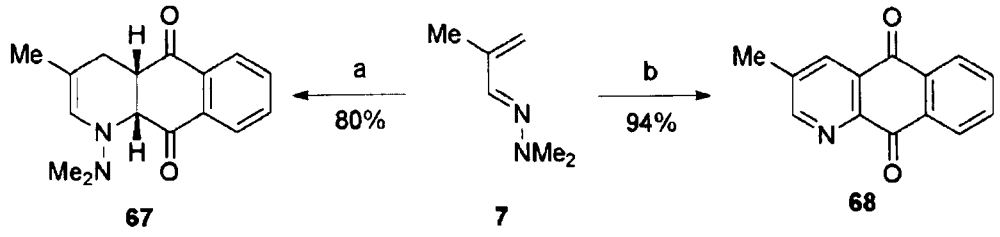
Cycloaddition of 3-siloxy-1-azadiene **37** with benzoquinone **63** afforded the dimethylamino-substituted product **66**, which also forms from displacement of the *tert*-butyldimethylsilyloxy group by the dimethylamine which is liberated in the aromatisation step (**Scheme 20**).[4]



37 63 66

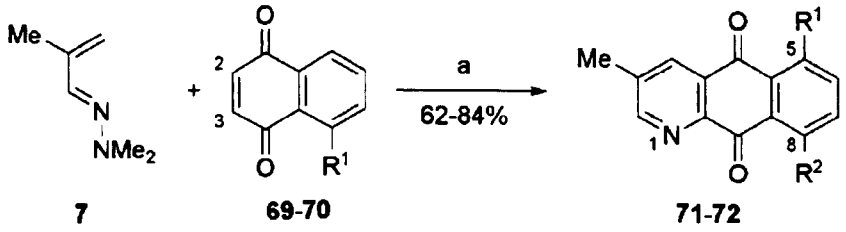
Scheme 20. *Reagents and conditions*: a. HF, MeCN, $CHCl_3$, H_2O, rt.

Ghosez and coworkers have also reported the use of naphthoquinone **50** as a dienophile. Cycloaddition under mild conditions afforded the tetrahydro-cycloadduct **67** in 80% yield by NMR analysis. The fully aromatised product **68** may be obtained in one pot by carrying out the reaction at higher temperature in the presence of palladium on charcoal (**Scheme 21**).[4, 22] Once again, ultrasonic irradiation has been employed in the formation of **67**, followed by air oxidation to **68** in 81% yield over 2 steps.[24]



Scheme 21. *Reagents and conditions*: a. naphthoquinone **50**, MeCN, -20 °C to rt; b. naphthoquinone **50**, 10% Pd/C, MeCN, 75 °C.

Potts *et al.* have shown that juglone **69** and its derivatives are also efficient dienophiles in the 1-aza-Diels-Alder reaction (**Scheme 22**). Thus, treatment of 1-azadiene **7** with juglone **69** afforded the 8-hydroxylated cycloadduct **71** with complete regiocontrol (**Table 8**, entry 1). This reactivity may be explained by the strong electron-withdrawing nature of the hydroxyl group on the adjacent carbonyl via hydrogen bonding, making C-2 electron-deficient.[34, 36] The opposite regiochemistry was obtained with methyljuglone **70** due to the electron-donating nature of the methoxy group (**Table 8**, entry 2).[37]

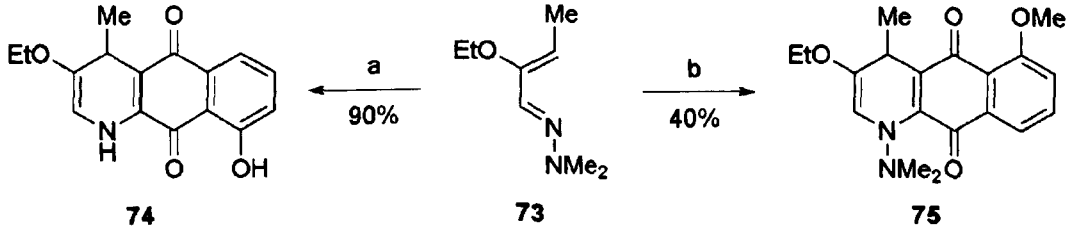


Scheme 22. *Reagents and conditions*: a. benzene, rt.

Table 8. Hetero-Diels-Alder reactions of hydrazone **7** with juglones **69-70**.

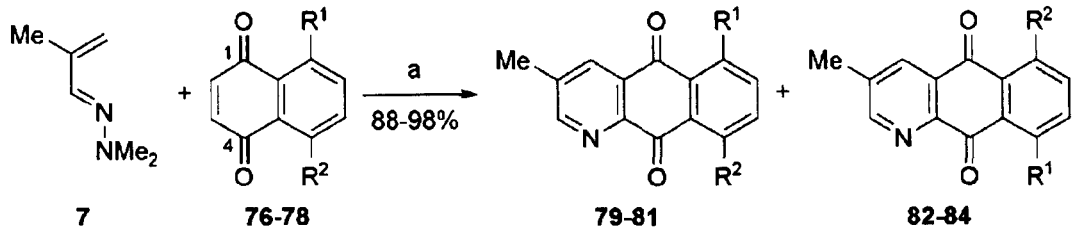
Entry	Dienophile	R^1	Product	R^1	R^2	Yield/%
1	**69**	OH	**71**	H	OH	84
2	**70**	OMe	**72**	OMe	H	62

The reaction of oxygenated 1-azadiene **73** with juglone **69** and its derivatives has been investigated under two sets of conditions (**Scheme 23**).[38, 39] Firstly, treatment of **73** with **69** in the presence of acetic anhydride proceeded with complete regioselectivity to give the dihydro-cycloadduct **74** in excellent yield. The role of acetic anhydride was to scavenge the dimethylamine liberated on cycloaddition, preventing it from adding to the starting quinone. In contrast, reaction of methyl juglone **70** with **73** in the presence of MnO_2 gave the *N*-dimethylamino dihydro-cycloadduct **75**. As expected, the methoxy group in methyl juglone **70** directs the cycloaddition with complete regioselectivity for the opposite isomer. In both cases, aromatisation to the pyridines was achieved on treatment with an appropriate oxidant.



Scheme 23. *Reagents and conditions*: a. juglone **69**, Ac_2O; b. methyljuglone **70**, MnO_2.

Unsymmetrical disubstituted naphthoquinones have also been used as dienophiles (**Scheme 24**).[40] With **76** as the dienophile, the reinforcing directing effects of the hydroxyl and methoxy groups gave the desired product as a single regioisomer **79** (**Table 9**, entry 1). A single regioisomer is also obtained with **77** (**Table 9**, entry 2).[41] The authors attributed this to the stronger hydrogen bonding between the hydroxyl group and its adjacent carbonyl compared to that between the amine group and its adjacent carbonyl. Competing activation of the C-1 and C-4 carbonyl groups in dienophile **78** leads to the formation of a mixture of cyclisation products **81** and **84**, although the hydroxyl group still dominates the regioselectivity (**Table 9**, entry 3).

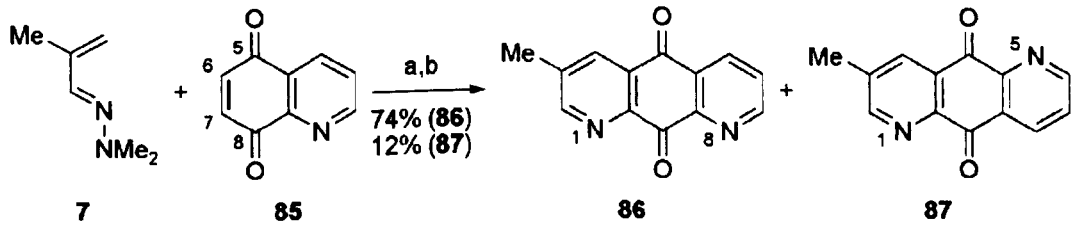


Scheme 24. *Reagents and conditions*: a. CH_2Cl_2, 8 h-20 d.

Table 9. Diels-Alder reaction of hydrazone **7** with disubstituted naphthoquinones **76-78**.

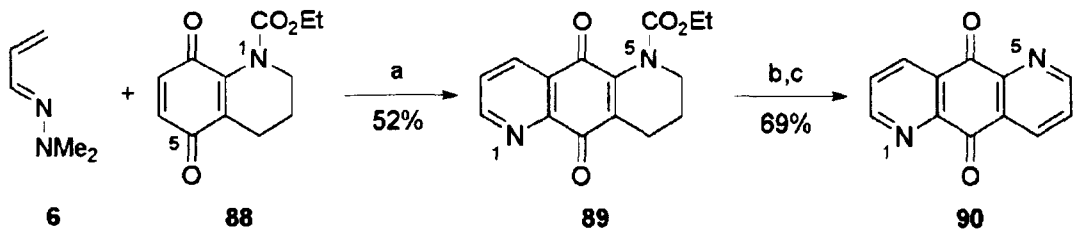
Entry	Dienophile	R^1	R^2	Yield/%	
1	**76**	OMe	OH	98 (**79**)	0 (**82**)
2	**77**	NH_2	OH	93 (**80**)	0 (**83**)
3	**78**	NHAc	OH	70 (**81**)	18 (**84**)

Treatment of 1-azadiene **7** with quinoline-5,8-dione **85** afforded predominantly the 1,8-diazaanthraquinone **86** after cycloaddition and oxidation (**Scheme 25**).[34, 36] The expected regioselectivity was obtained by virtue of the electron-withdrawing effect of the ring nitrogen atom on the C-8 carbonyl, directing attack of the C-4 end of the diene to C-6 of the dienophile. Application of ultrasonic conditions to the formation of **86** led to a decrease in reaction time, but with a loss of regioselectivity.[24]



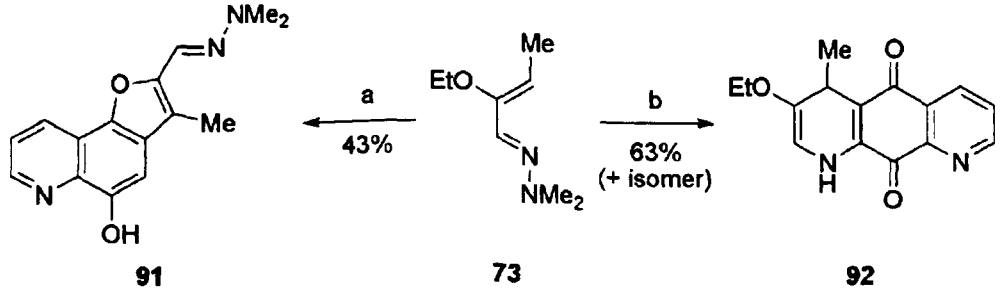
Scheme 25. *Reagents and conditions*: a. benzene, rt, 12 h; b. EtOH, reflux, 2 h.

Opposite regioselectivity may be obtained by choosing a dienophile system that overrides the effect of the ring nitrogen atom and makes the C-5 carbonyl more electron-deficient. Thus, the ethoxycarbonyl group in tetrahydroquinoline-5,8-dione **88** promotes the exclusive formation of the 1,5-isomer **90** after cycloaddition, deprotection and oxidation (**Scheme 26**).[42]



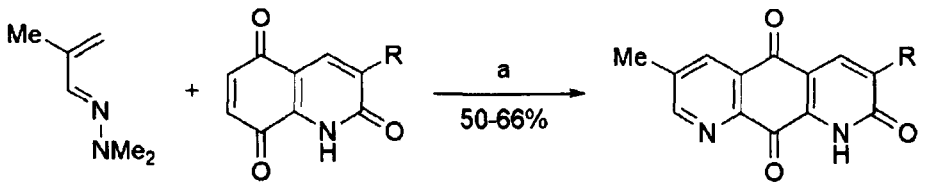
Scheme 26. *Reagents and conditions*: a. CH_2Cl_2, rt, 16 h; b. deprotection; c. DDQ

The 1-aza-Diels-Alder reaction between diene **73** and quinoline-5,8-dione **85** has also been studied in detail. Interestingly, traces of acid and oxygen accelerated a competing stepwise process, affording the furoquinoline **91** as the major product, with only small amounts (8%) of the desired [4+2]-cycloadduct (**Scheme 27**). The desired [4+2]-dihydro-cycloadduct **92** was obtained in 63 % yield (3:2 mixture of regioisomers) by carrying out the reaction in degassed toluene under nitrogen.[39, 43, 44]



Scheme 27. *Reagents and conditions*: a. quinoline-5,8-dione **85**, $CHCl_3$, rt, 1 h; b. quinoline-5,8-dione **85**, toluene (degassed), rt 15 min.

Hetero-Diels-Alder reaction between 1-azadiene **7** and quinoline-2,5,8-triones **93-97** substituted with a variety of groups at C-3 proceeded with complete regioselectivity to give the aromatic cycloadducts **98-102** (**Scheme 28, Table 10**). As expected, the regiochemistry is controlled by the presence of the amide nitrogen and the C-2 carbonyl.[45]



7 **93-97** **98-102**

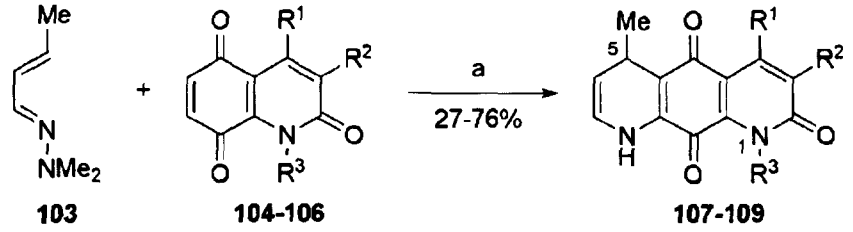
Scheme 28. *Reagents and conditions*: a. $CHCl_3$ or THF, rt, 5-45 min.

Table 10. Hetero-Diels-Alder reaction between hydrazone **7** and quinoline-2,5,8-triones **93-97**.

Entry	Dienophile	R	Product	Yield/%
1	**93**	Me	**98**	50
2	**94**	Ph	**99**	50
3	**95**	CHO	**100**	51
4	**96**	COMe	**101**	62
5	**97**	CO_2H	**102**	66

In contrast, Diels-Alder cycloaddition of 1-azadiene **103**, substituted with a methyl group at C-4, afforded the dihydro-cycloadducts **107-109** as the major products (**Scheme 29, Table 11**).[45-47] This may be attributed to the increased steric interaction of the C-5 substituent with the adjacent carbonyl in the planar aromatic product. In many cases, addition of dimethylamine (liberated during the reaction) to the starting quinone was observed, giving rise to the moderate yields. Addition of a chloroformyl-

polystyrene resin or silica gel has been used to suppress by-product formation, leading to increased yields (80-90%).[35, 48]

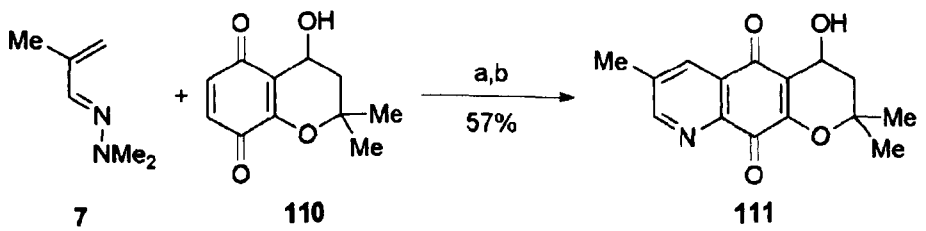


Scheme 29. *Reagents and conditions*: a. $CHCl_3$, rt.

Table 11. Hetero-Diels-Alder reaction of hydrazone **103** with quinoline-2,5,8-triones **104-106**.

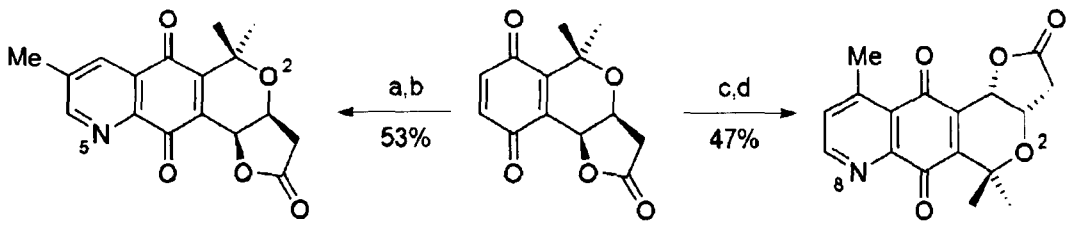
Entry	Dienophile	R^1	R^2	R^3	Product	Yield/%
1	**104**	Me	H	H	**107**	51
2	**105**	H	Et	H	**108**	27
3	**106**	CH_2OAc	H	Me	**109**	76

Treatment of substituted chromanquinone **110** with 1-azadiene **7** gave the aromatic product **111** after cycloaddition and *in situ* oxidation (**Scheme 30**). The observed regiochemistry is controlled by electron donation from the ring oxygen atom. Hydrogen bonding between the hydroxyl group and the C-5 carbonyl is unfavourable as they are not coplanar, hence cannot influence the regiochemical outcome.[49]



Scheme 30. *Reagents and conditions*: a. CH_2Cl_2, rt, 3 h; b. Ag_2O, SiO_2 or DDQ.

Läckner has shown that the regioselectivity in the hetero-Diels-Alder of isochromanquinone **112** may be controlled by the substitution pattern of the diene. Thus, 1-azadienes lacking a substituent at C-4 gave the 2,5-cycloadduct **113** after cycloaddition and subsequent oxidation with MnO_2, whilst diene **103** afforded the 2,8-isomer **114** (**Scheme 31**).[50]

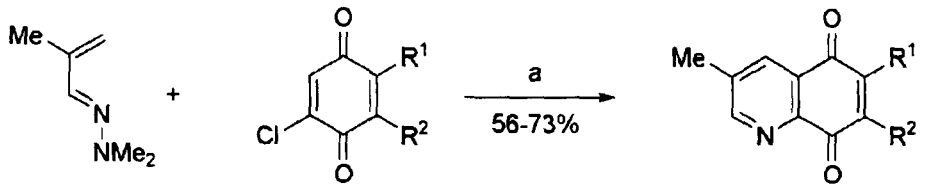


113 **112** **114**

Scheme 31. *Reagents and conditions*: a. **7**, benzene, rt, 18 h; b. MnO_2, $CHCl_3$; c. **103**, benzene, rt, 18 h; d. MnO_2, $CHCl_3$.

Hetero-Diels-Alder reactions involving unsymmetrical dienophiles often lead to mixtures of regioisomeric products. One of the most successful ways to combat this problem is the incorporation of a halogen atom into the dienophile. Frequently this allows selective formation of both regioisomers, without the need for complicated separations.

For example, treatment of 1-azadiene **7** with chloroquinones **115-118** gave the aromatic products **119-122** in moderate to good yield as single regioisomers (**Scheme 32, Table 12**). In each case, the C-4 end of the diene is directed to the less hindered end of the dienophile.[51]

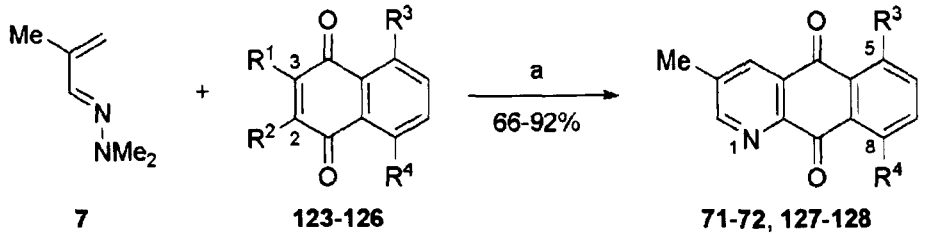


Scheme 32. *Reagents and conditions*: a. CH_2Cl_2, rt.

Table 12. Hetero-Diels-Alder reaction of hydrazone **7** with chloroquinones **115-118**.

Entry	Dienophile	R^1	R^2	Product	Yield/%
1	**115**	H	Cl	**119**	56
2	**116**	Cl	H	**120**	71
3	**117**	H	OMe	**121**	73
4	**118**	OMe	H	**122**	73

Chlorinated analogues of juglone and methyl juglone allow formation of both the 5- and 8-substituted cycloadducts with 1-azadiene **7**. As was shown in **Scheme 22**, the hydroxyl group in juglone **69** and the methoxy group in methyljuglone **70** control the regiochemistry under normal conditions, leading to selective formation of the 8- and 5-substituted products respectively. However, introduction of a halogen at C-2 or C-3 of the dienophile exerts stronger regiochemical control than that of the C-5 substituent (**Scheme 33**). Thus, C-2 halogenated dienophiles **123** and **125** allow selective formation of the 8-substituted products (**Table 13**, entries 1 and 3). The opposite regioisomers **127** and **72** were obtained from the C-3 halogenated dienophiles **124** and **126** (**Table 13**, entries 2 and 4). As with the chlorobenzoquinone dienophiles, the C-4 (electron-rich) end of the diene attacks the unsubstituted end of the dienophile.[51]

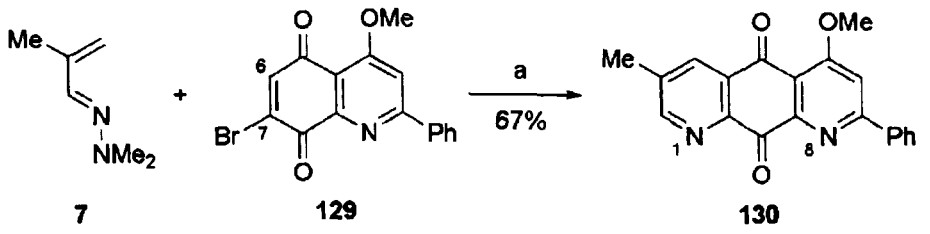


Scheme 33. *Reagents and conditions*: a. CH_2Cl_2 or MeCN, rt, 48-120 h.

Table 13. Hetero-Diels-Alder reaction of hydrazone 7 with chlorinated juglones **123-126**.

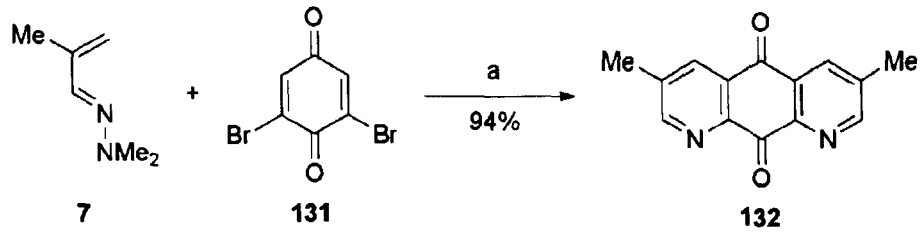
Entry		Dienophile					Product		Yield
		R^1	R^2	R^3	R^4		R^3	R^4	
1	**123**	H	Cl	H	OH	**71**	H	OH	67
2	**124**	Cl	H	H	OH	**127**	OH	H	92
3	**125**	H	Cl	H	OMe	**128**	H	OMe	70
4	**126**	Cl	H	H	OMe	**72**	OMe	H	66

Diazaanthraquinones may also be formed selectively via a halogenated dienophile approach. For example, 1,8-diazaanthraquinone **130** was synthesised from 7-bromo-4-methoxy-2-phenylquinoline-5,8-dione **129** (**Scheme 34**). The opposite regioisomer was obtained in 50% yield from 6-bromo-4-methoxy-2-phenylquinoline-5,8-dione.[52]



Scheme 34. *Reagents and conditions*: a. benzene, rt, 15 min.

Finally, a double hetero-Diels-Alder reaction may be carried out with the appropriately substituted dienophile such as 2,6-dibromobenzoquinone **131** to give 3,6-dimethyl-1,8-diazaanthraquinone **132** (**Scheme 35**).[53]

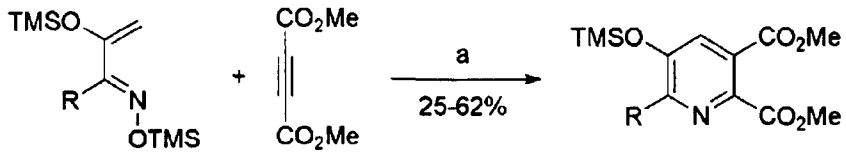


Scheme 35. *Reagents and conditions*: a. CH_2Cl_2, rt, 1 min.

1.3 Hetero-Diels-Alder Reactions of Electron-Rich 1-Azadienes with Acetylenes

Many examples of 1-aza-Diels-Alder reactions are known where the dihydro- or tetrahydropyridine cycloadduct is isolated directly from the cycloaddition. Formation of the aromatic product is usually achieved in a separate step through treatment with a suitable oxidising agent, typically activated MnO_2 or palladium on charcoal. One method for the formation of the aromatic products in one pot is to use an acetylenic dienophile instead of an alkene.

Furukawa *et al.* first reported the reaction of a range of 3-siloxy-1-aza-1,3-butadienes **133-135** (readily prepared from the α-ketoximes on treatment with trimethylchlorosilane, sodium iodide and base) with dimethyl acetylenedicarboxylate (DMAD) **136** (**Scheme 36**).[54] A poor yield was obtained with the C-2 unsubstituted diene **133** (**Table 14**, entry 1), which may be due to the instability of either the starting material or product under the reaction conditions. Introduction of a methyl or methoxycarbonyl substituent raised the yield considerably (**Table 14**, entries 2-3), in contrast to the trend observed with the equivalent *N*,*N*-dimethylhydrazones. Hetero-Diels-Alder reaction of a 1-azadiene substituted with a methyl group at C-3 was also investigated, although no product was observed after 48 hours under reflux in toluene.

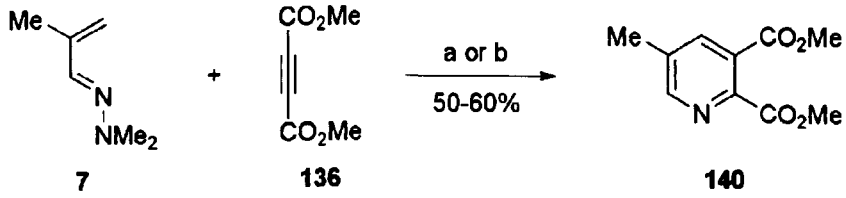


Scheme 36. *Reagents and conditions*: a. benzene, reflux, 8 h.

Table 14. Hetero-Diels-Alder reaction of oximes **133-135** with DMAD **136**.

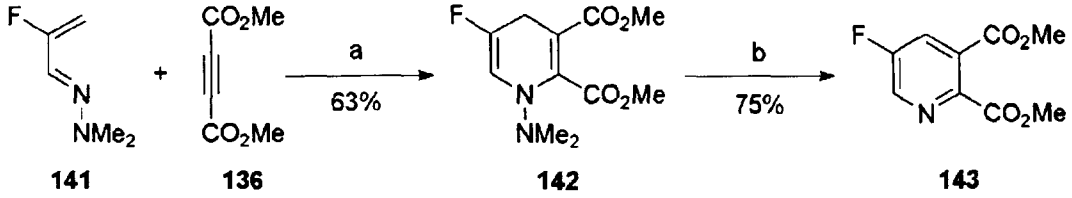
Entry	1-Azadiene	R	Product	Yield/%
1	**133**	H	**137**	25
2	**134**	Me	**138**	60
3	**135**	CO_2Me	**139**	62

A further example is the [4+2]-cycloaddition of 1-azadiene **7** with DMAD **136**. Although no reaction occurred under standard thermal heating,[4] both ultrasonic[24] and microwave[55] irradiation have been successfully employed to afford the desired pyridine dicarboxylate **140** in 60% and 50% yield respectively (**Scheme 37**).



Scheme 37. *Reagents and conditions*: a. ultrasound, 50 °C, 50 h; b. MW, Et_2O, 10 min.

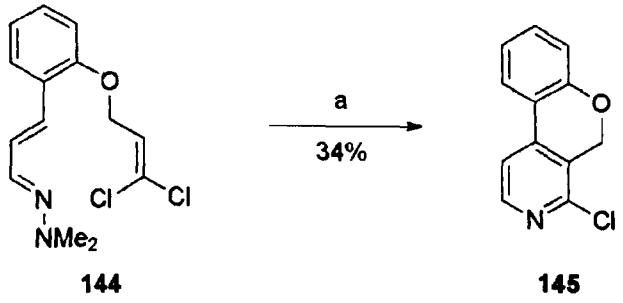
Unlike **7**, the fluorinated 1-azadiene **141** reacted with DMAD **136** under normal thermal conditions. However, the initial product isolated was the stable dihydro-cycloadduct **142**, which had to be aromatised to the pyridine **143** by elimination of dimethylamine on treatment with acid (**Scheme 38**).[56]



Scheme 38. *Reagents and conditions*: a. toluene, 80 °C, 50 h; b. toluene, HCl, rt, 45 min.

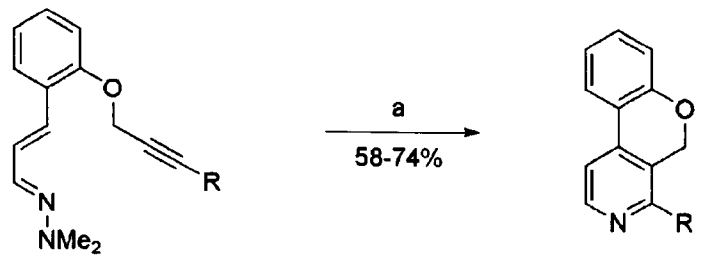
1.4 Intramolecular Hetero-Diels-Alder Reactions of Electron-Rich 1-Azadienes

The first example of an intramolecular hetero-Diels-Alder (IMDA) reaction of α,β-unsaturated hydrazones was reported by Dolle and coworkers in 1988. Although [4+2]-cyclisation failed to take place with an unsubstituted allyl ether due to a competing [3,3]-Claisen rearrangement, incorporation of halogens into the dienophile portion allowed smooth reaction to take place (**Scheme 39**).[57]



Scheme 39. *Reagents and conditions*: a. xylene, reflux, 48 h.

The same authors reported two examples of IMDA reactions involving acetylenic dienophiles. Thus, cyclisation was induced on heating in xylene to give the expected pyridines **148-149** after 18 hours (**Scheme 40**, **Table 15**).[57]



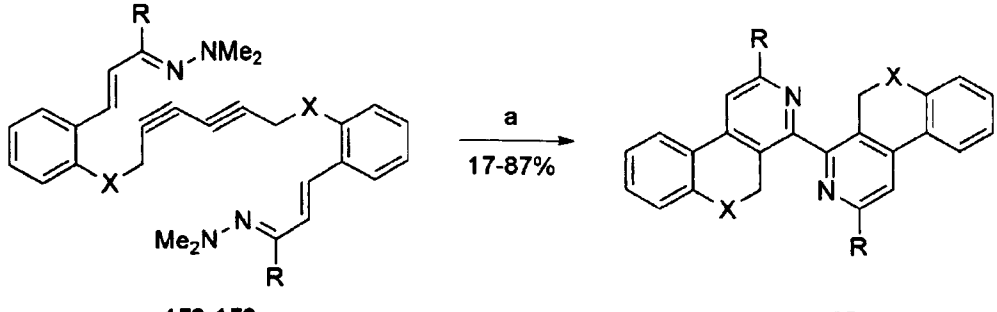
146-147 148-149

Scheme 40. *Reagents and conditions*: a. xylene, reflux, 18 h.

Table 15. IMDA cycloadditions of hydrazones **146-147**.

Entry	Substrate	R	Product	Yield/%
1	**146**	H	**148**	58
2	**147**	Ph	**149**	74

Moody and coworkers have exploited a double hetero-Diels-Alder reaction of aromatic ethers and amides as a novel route to 2,2'-bipyridines (**Scheme 41**, **Table 16**). Once again, a lower yield was observed where the 1-azadiene was substituted at the C-2 position (**Table 16**, entry 2).[58, 59]



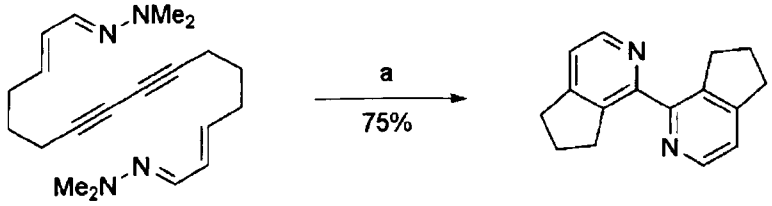
150-152 153-155

Scheme 41. *Reagents and conditions*: a. xylene or mesitylene, reflux. Alkynes drawn non-linear for clarity.

Table 16. IMDA cycloadditions of hydrazones **150-152.**

Entry	Substrate	R	X	Product	Yield/%
1	**150**	H	O	**153**	87
2	**151**	Me	O	**154**	17
3	**152**	H	NBz	**155**	68

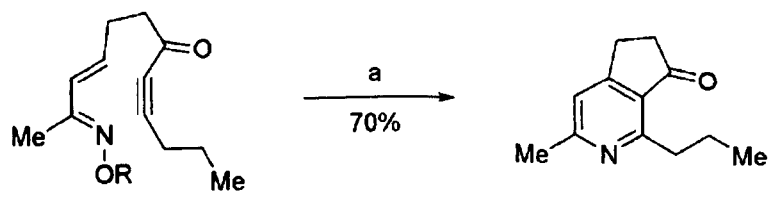
The double IMDA reaction of unsaturated *N,N*-dimethylhydazones linked through an aliphatic chain was also shown to proceed in good yield (**Scheme 42**).[58, 59]



156 **157**

Scheme 42. *Reagents and conditions*: a. xylene, reflux.

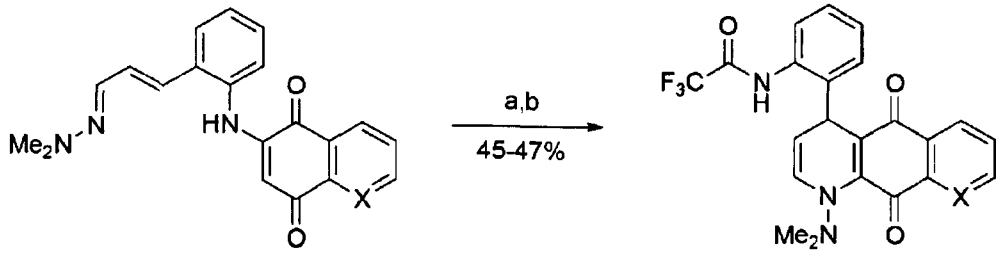
Boger and coworkers have utilised an intramolecular hetero-Diels-Alder reaction of *O*-alkyl α,β-unsaturated oximes **158-159** as the key step in their synthesis of the tropoloalkaloid rubrolone **160**. Although no reaction was observed at temperatures below 140 °C, cyclisation was subsequently found to occur between 175-185 °C using triisopropylbenzene as the solvent (**Scheme 43**).[60]



158-159 **160**

Scheme 43. **158**: R=Me, **159**: R=Bn; *Reagents and conditions*: a. triisopropylbenzene, 175-185 °C, 36 h.

Quinonic dienophiles have also been investigated in the intramolecular 1-aza-Diels-Alder reaction, through activation of the secondary nitrogen as the trifluoroacetamide, followed by cycloaddition and elimination (**Scheme 44**, **Table 17**).[61]



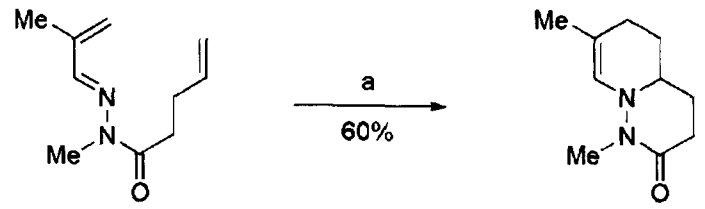
161-162 **163-164**

Scheme 44. *Reagents and conditions*: a. NaH, TFAA, THF, rt; b. TFA, CH_2Cl_2, rt, 1 h.

Table 17. IMDA cycloadditions of hydrazones **161-162**.

Entry	Substrate	X	Product	Yield/%
1	**161**	CH	**163**	45
2	**162**	N	**164**	47

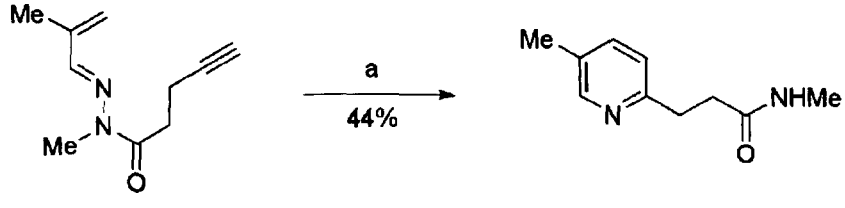
Gilchrist *et al.* have reported acyl hydrazones as efficient systems in intramolecular Diels-Alder reactions. For instance, unsaturated hydrazone **165** undergoes cycloaddition under reflux in *o*-dichlorobenzene in good yield (**Scheme 45**). The presence of an alkyl substituent at C-3 in the diene fragment was found to be crucial, as the corresponding compound with a proton at this position failed to cyclise at temperatures up to 180 °C, and decomposed above this.[28, 29] This observation is in accordance with the results reported by Ghosez and others.



165 166

Scheme 45. *Reagents and conditions*: a. *o*-DCB, reflux, 48 h.

Once again, introduction of an acetylenic dienophile afforded the 2,5-disubstituted pyridine after heating in *o*-dichlorobenzene for 2 days (**Scheme 46**). Analogous unsaturated oximes were found to be unreactive compared to the acylhydrazones, which was attributed to superior electron donation of the acylamino substituent into the diene.[28, 29]

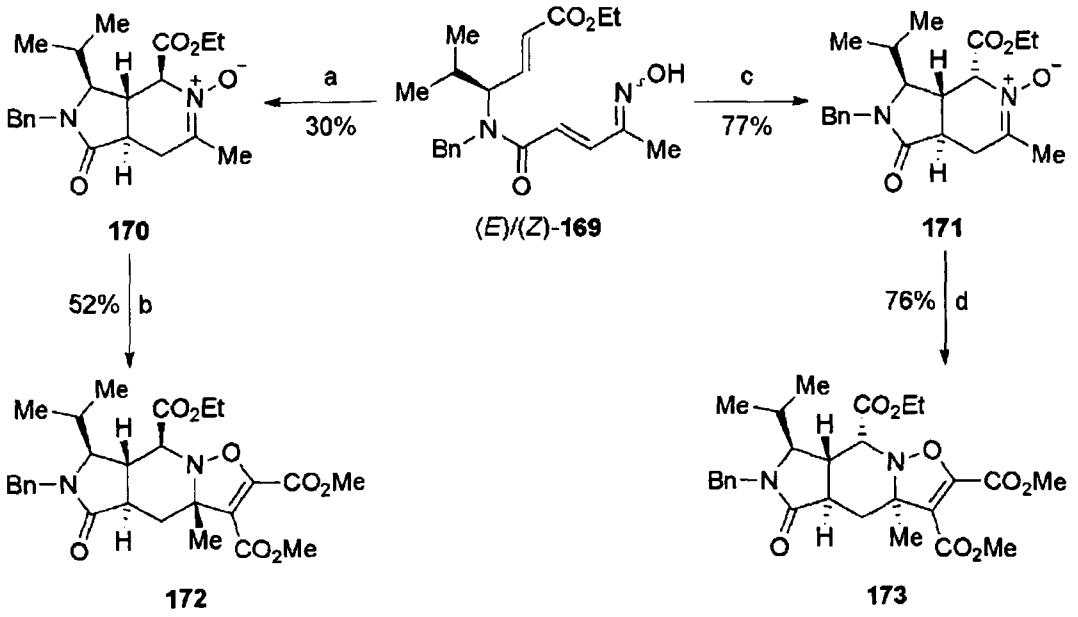


167 168

Scheme 46. *Reagents and conditions*: a. *o*-DCB, reflux, 48 h.

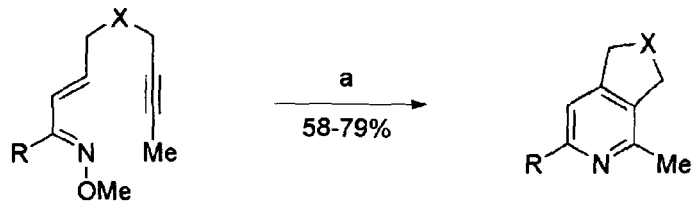
The IMDA reaction of α,β-unsaturated oximes **169** to give the corresponding nitrones **170-171** has been explored. Thus, intramolecular cycloaddition of (*E*)-**169** gave nitrone **170** as a single isomer in 30% yield. Subsequent treatment with DMAD **136** led to formation of the tricyclic product **172** as the only isolable product (**Scheme 47**). The observed stereoselectivity is dictated by the proximal ester group, which directs the approach of the dipolarophile to the less hindered lower (*re*) face. The opposite nitrone diastereomer **171** was obtained by heating (*Z*)-**169** in glacial acetic acid. Subsequent 1,3-dipolar cycloaddition gave a 1:0.28 mixture of the two possible

stereoisomers **173**, which was attributed to partial blocking of the upper (*si*) face by the remote isopropyl group.[62]



Scheme 47. *Reagents and conditions*: a. (*E*)-**169**, CH_2Cl_2, rt, 4 d; b. DMAD **136**, toluene, rt, 30 min; c. (*Z*)-**169**, AcOH, 100 °C, 4 h; d. DMAD **136**, toluene, 65 °C, 2 h (major isomer shown).

Saito and coworkers have recently reported the Rh(I)-catalysed IMDA reaction of various ω-alkynyl-vinyl oximes in the formation of bicyclic pyridines. An optimised catalyst system of 5 mol% $[RhCl(cod)]_2$ and 13 mol% $AgSbF_6$ in hexafluoroisopropanol (HFIP) was found to promote facile cycloaddition of ω-alkynyl-vinyl oximes **174-176** to the desired annulated pyridines **177-179** in 58-79% yield (**Scheme 48**, **Table 18**). Terminal acetylenes however failed to cyclise under the same conditions.[63]



174-176 177-179

Scheme 48. *Reagents and conditions*: a. 5 mol% $[RhCl(cod)]_2$, 13 mol% $AgSbF_6$, HFIP, rt-80 °C, 3-23 h.

Table 18. Rh(I)-catalysed IMDA reactions of ω-alkynyl-vinyl oximes **174-176**.

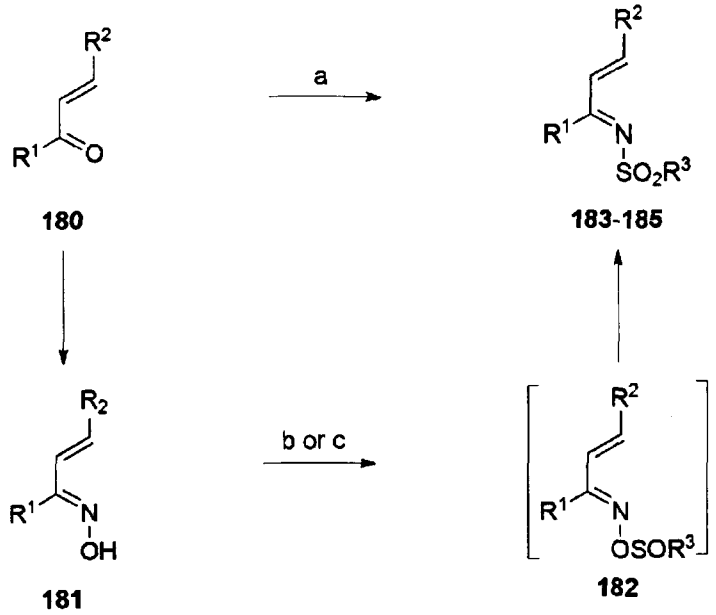
Entry	Substrate	R	X	Product	Yield/%
1	**174**	Me	O	**177**	79
2	**175**	Me	NTs	**178**	58
3	**176**	Ph	NTs	**179**	61

1.5 Inverse Electron-Demand 1-Aza-Diels-Alder Reactions

The synthetic application of inverse electron-demand 1-aza-Diels-Alder reactions has been pioneered primarily by Boger[9-15] and Fowler.[16-21] In an extensive series of studies, Boger and coworkers have shown that various *N*-benzenesulfonylimines act as efficient 1-azadienes with a range of electron-rich dienophiles. Such is the effect of the *N*-benzenesulfonyl group on the activation of the 1-azadiene that reactions are routinely performed at room temperature or below.

The required hetero-Diels-Alder substrates **183-185** were prepared either from the α,β-unsaturated ketones **180** by direct condensation with an arylsulfonamide (method a), or from the free oximes **181** by homolytic rearrangement of their *O*-sulfinyl derivatives **182** formed *in situ* using either an arylsulfinyl chloride (method b) or

sulfonyl cyanide (method c) and triethylamine as reagents (**Scheme 49**). Some examples of 1-azadienes prepared in this way are shown in **Table 19**.

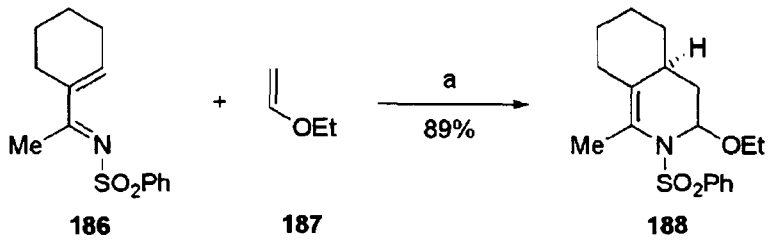


Scheme 49. *Reagents and conditions*: a. $R^3SO_2NH_2$, $MgSO_4$, toluene or $TiCl_4$, CH_2Cl_2; b. R^3SOCl, Et_3N, CCl_4, 0 °C to rt, 12 h; c. R^3SO_2CN, Et_3N, CCl_4, 0 °C to rt, 10 h.

Table 19. Preparation of *N*-sulfonyl-1-aza-1,3-butadienes **183-185**.

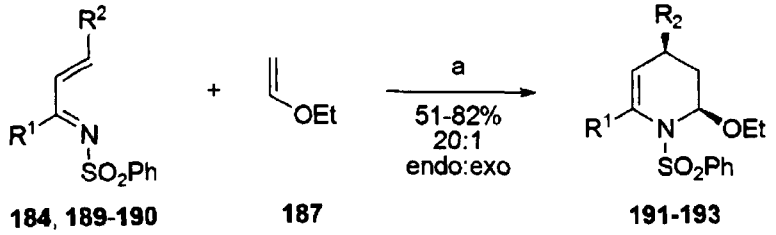
Entry	Method	R^1	R^2	R^3	Product	Yield/%
1	a	H	Ph	Ph	**183**	50%
2	b	CO_2Et	Ph	Ph	**184**	69%
3	c	Me	Ph	*p*-Tol	**185**	63%

Treatment of *N*-sulfonyl-1-azadiene **186**, prepared using the above methodology, with ethyl vinyl ether **187** in dichloromethane gave the tetrahydro-cycloadduct **188** in excellent yield (**Scheme 50**). The corresponding free oxime and *O*-methyl oxime failed to react under the same conditions.[9]



Scheme 50. *Reagents and conditions*: a. CH_2Cl_2, 12 kbar, rt.

Incorporation of a noncomplementary electron-withdrawing group into the 1-azadiene further accelerates their reaction with electron-rich dienophiles, such as the hetero-Diels-Alder reaction of ethoxycarbonyl-substituted dienes **184** and **189-190** with ethyl vinyl ether **187** (**Scheme 51**, **Table 20**).[11, 12]



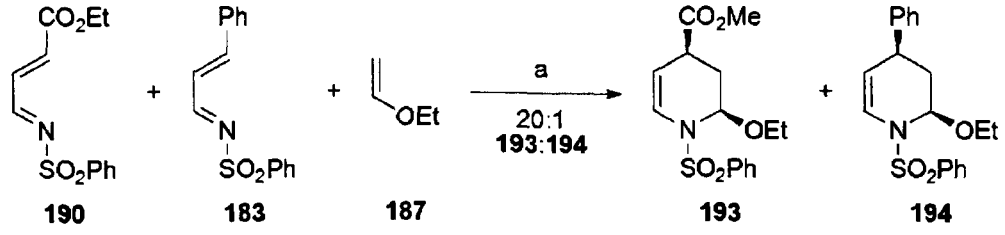
Scheme 51. *Reagents and conditions*: a. CH_2Cl_2, rt, 24 h.

Table 20. Diels-Alder reaction of 1-azadienes **184** and **189-190** with ethyl vinyl ether **187**.

Entry	1-Azadiene	R^1	R^2	Product	Yield/%
1	**189**	CO_2Et	Me	**191**	80
2	**184**	CO_2Et	Ph	**192**	51
3	**190**	H	CO_2Et	**193**	82

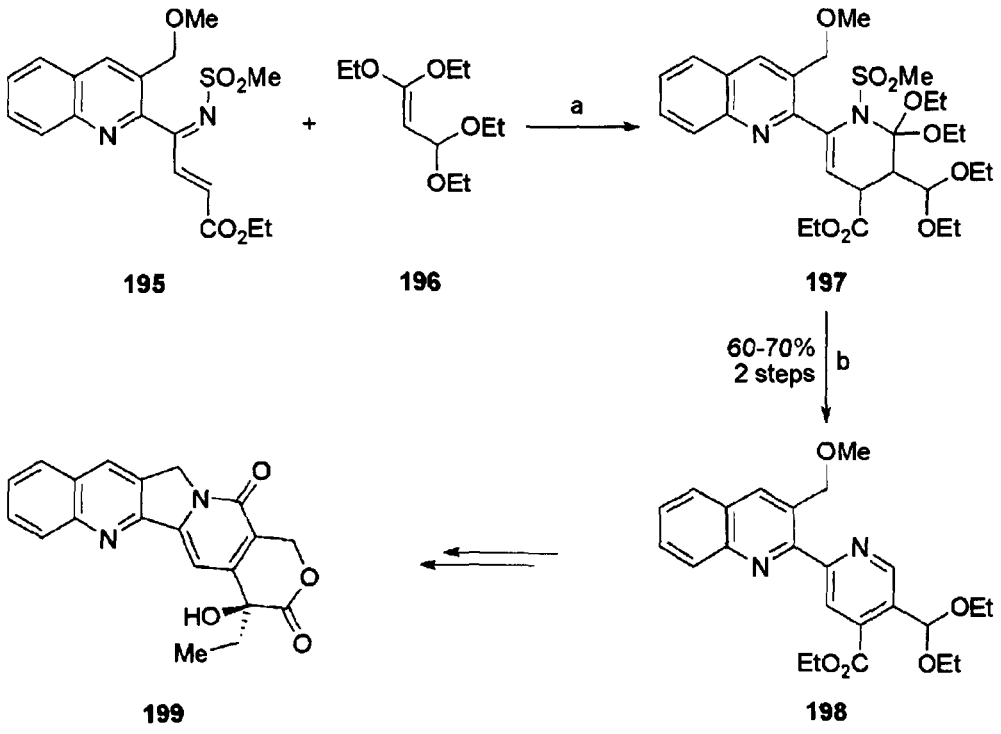
This rate enhancement was further demonstrated by competition experiments between 4-ethoxycarbonyl-*N*-sulfonyl-1-azadiene **190** and 4-phenyl-*N*-sulfonyl-1-azadiene **183** for the same dienophile (**Scheme 52**). The product distribution was shown to be >20:1 in favour of the ethoxycarbonyl-substituted product **193**. Similar results were obtained

for competition experiments involving 2-ethoxycarbonyl-*N*-sulfonyl-1-aza-1,3-butadiene.[11]



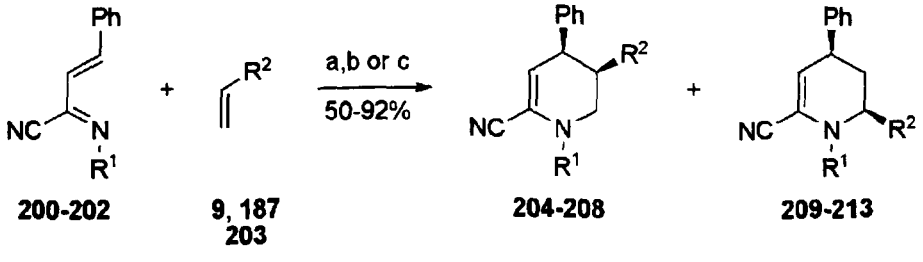
Scheme 52. *Reagents and conditions*: a. CH_2Cl_2, rt.

Boger and coworkers have applied this methodology towards the total synthesis of a number of complex natural products, including (+)-camptothecin **199**. The key inverse electron-demand Diels-Alder reaction was carried out between *N*-sulfonyl-1-azadiene **195** and 1,1,3,3-tetraethoxypropene **196**, followed by aromatisation to give the trisubstituted pyridine **198** in 60-70% yield, which was further converted to the natural product (**Scheme 53**).[64]



Scheme 53. *Reagents and conditions*: a. benzene, rt, 4 h; b. NaOEt, EtOH, THF, 0 °C, 75 min.

Fowler and coworkers have successfully demonstrated that incorporation of a 2-cyano group renders the 1-azadiene (prepared by addition of trimethyl cyanide into the imine) sufficiently reactive to undergo hetero-Diels-Alder cycloaddition with a range of dienophiles, including electron-rich and electron-poor alkenes (**Scheme 54**, **Table 21**). The reaction proceeds with high levels of *endo* selectivity to give the *cis*-substituted products **204-213**.[18, 19]



Scheme 54. *Reagents and conditions*: a. benzene, rt to reflux, 24-48 h; b. neat, rt to reflux, 24-48 h; c. neat, 110 °C, 8 d.

Table 21. Hetero-Diels-Alder reactions of 2-cyano-1-azadienes **196-198**.

Entry	1-Azadiene	R^1	Dienophile	R^2	Yield/%	
1	**200**	OAc	**203**	Ph	79(**204**)	13 (**209**)
2	**200**	OAc	**187**	OEt	0 (**205**)	69 (**210**)
3	**200**	OAc	**9**	CO_2Me	0 (**206**)	92 (**211**)
4	**201**	CO_2Me	**187**	OEt	0 (**207**)	92 (**212**)
5	**202**	Ph	**203**	Ph	0 (**208**)	50 (**213**)

Frontier orbital calculations have confirmed that cycloadditions between 1-azadienes **200-202** and electron-rich dienophiles do indeed proceed via an inverse electron-demand process. Further evidence for this is the complete *endo*- and regioselectivity observed in these reactions. In contrast, cycloadditions between 1-azadienes **200-202** and electron-deficient dienophiles are most likely normal electron-demand reactions, often leading to a mixture of regioisomers.[16]

1.6 Conclusions

The 1-aza-Diels-Alder reaction has been shown to be an efficient and versatile method for the preparation of a large variety of nitrogen-containing six-membered heterocycles. The cycloaddition of electron-rich 1-aza-1,3-butadienes with alkene dienophiles has been extensively examined to give the dihydro- or tetrahydropyridine cycloadducts. Oxidation to the corresponding pyridines was frequently achieved using oxidants such as manganese dioxide or palladium on charcoal. Alkyne dienophiles have also been employed in the hetero-Diels-Alder reaction, allowing formation of the aromatic products directly from the reaction mixture.

The use of benzoquinone dienophiles has often been hampered by addition of nucleophilic amines (liberated on aromatisation during the reaction) into both the starting material and product. This problem has been solved by the addition of an appropriate amine scavenger into the reaction medium. The observed regiochemistry is often controlled by the electronic properties of the quinonic dienophile. Incorporation of a halogen atom into the quinone double bond has proved a valuable strategy to achieve complete regiocontrol. Several examples of intramolecular hetero-Diels-Alder reactions involving both alkene and alkyne dienophiles have also been reported.

The inverse electron-demand hetero-Diels-Alder reaction of *N*-sulfonyl- and 2-cyano-1-azadienes with electron-rich dienophiles has been explored by Boger and Fowler respectively. Excellent yields and high degrees of *endo* selectivity were observed in a range of cases. This methodology has subsequently been employed in the synthesis of several complex natural products.

Chapter 2

Results and Discussion

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Intermolecular 1-Aza-Diels-Alder Reactions

2.1 Introduction

The pyridine ring appears in a range of bioactive compounds, both naturally occurring and synthetic, often in highly substituted form; examples of particular interest to our research group include the thiopeptide antibiotic nosiheptide **214** and the antitumour antibiotic streptonigrin **215** (**Figure 6**). Although focus will remain on synthetic efforts towards streptonigrin **215**, a brief study on model systems related to the tetra-substituted pyridine core of nosiheptide **214** will also be presented.

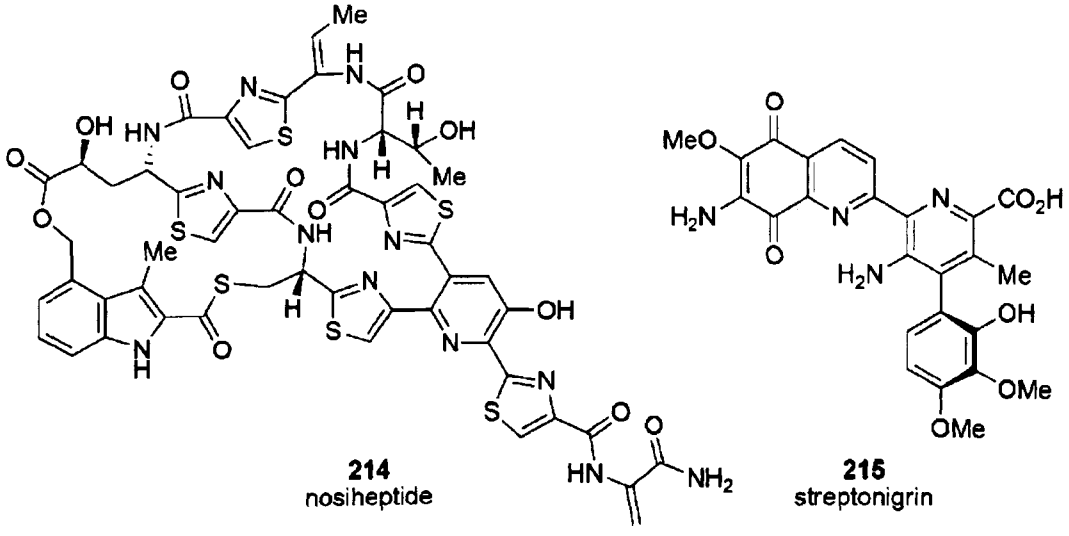
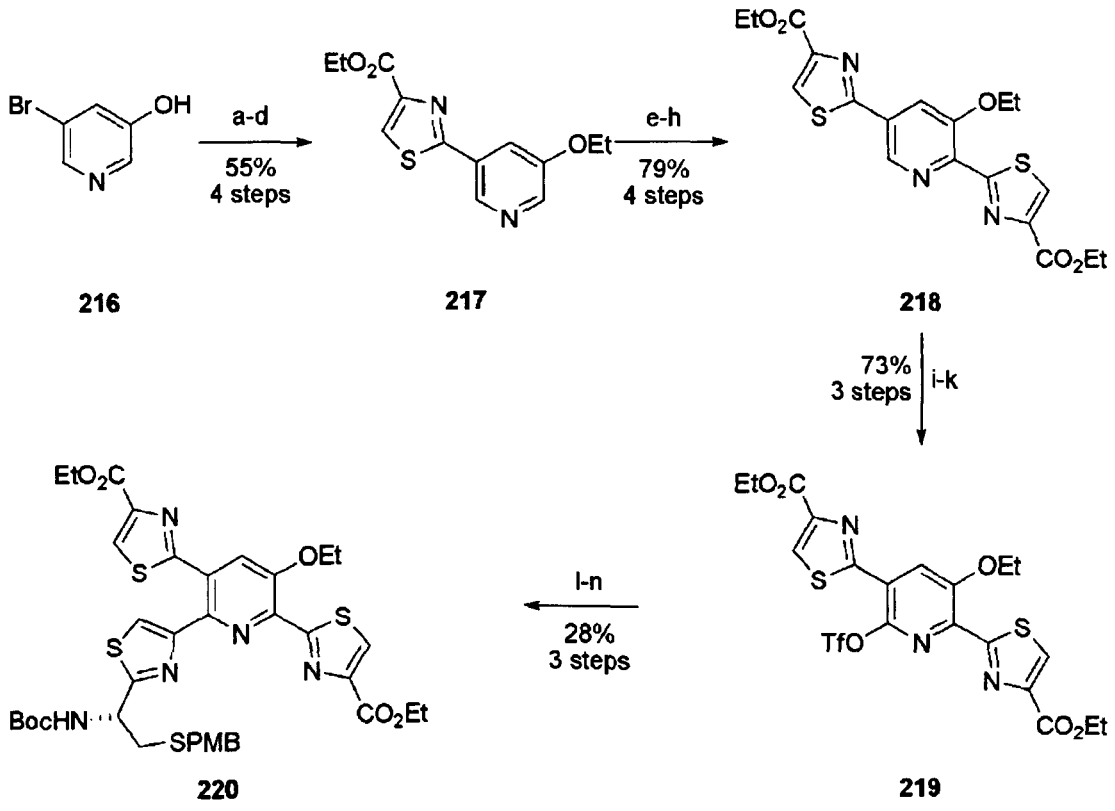


Figure 6.

Nosiheptide **214** is a member of the thiopeptide antibiotics, a class of sulfur containing highly modified cyclic peptides characterised by the presence of a heterocyclic centrepiece consisting of a tri- or tetra-substituted pyridine embedded in a macrocyclic array.[65]

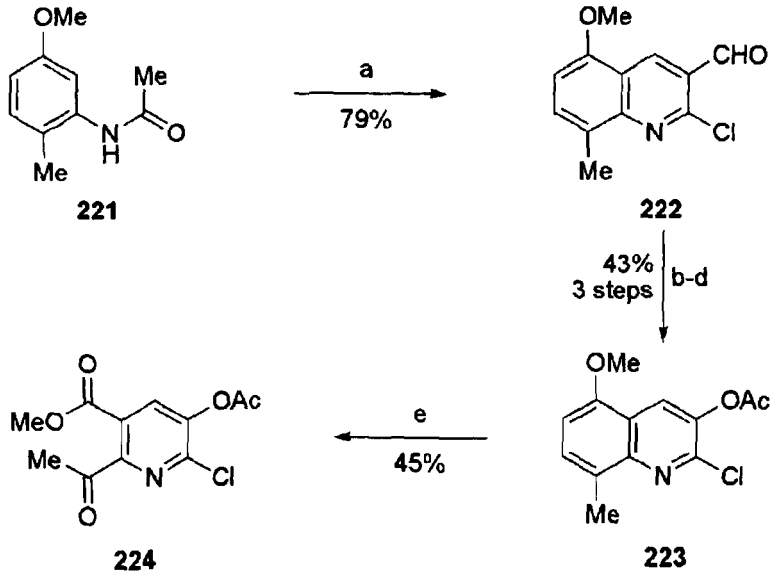
The natural product was first isolated from *Streptomyces actuous* 40037 in 1961,[15, 66] and was characterised through degradation[67] and X-ray crystallographic studies.[68, 69] Nosiheptide **214** is currently used commercially as a feed additive to promote weight gain in poultry and pigs.[70, 71]

Although nosiheptide **214** has yet to succumb to total synthesis, several approaches to various fragments, including the pyridine core, have been reported.[72-81] Shin and coworkers first completed the tetra-substituted pyridine unit **220** of nosiheptide **214** in stepwise fashion starting from 5-bromo-3-hydroxypyridine **216** (**Scheme 55**). Key steps in this synthesis included the conversion of a C-5 cyano group into the thioamide and subsequent Hantzsch reaction to form the 5-thiazoyl pyridine **217**. A Reissert reaction was used to install a second cyano group at C-2, followed by conversion into 2-thiazoyl pyridine **218** as before. A further Reissert reaction was employed to form the pyridone, which was converted into the third thiazoyl unit via triflation, Stille cross-coupling, bromination and a final Hantzsch reaction to give protected pyridine **220**.[76, 77]



Scheme 55. *Reagents and conditions*: a. CuCN, DMF, reflux; b. Et_2SO_4, K_2CO_3, DMF, reflux; c. H_2S, pyridine, Et_3N; d. EtO_2CCOCH_2Br, EtOH; e. *m*-CPBA, CH_2Cl_2; f. TMSCN, Et_3N, MeCN, reflux; g. H_2S, pyridine, Et_3N; h. EtO_2CCOCH_2Br, K_2CO_3, THF, 0 °C then TFAA, pyridine, THF, 0 °C; i. *m*-CPBA, CH_2Cl_2; j. Ac_2O, 100 °C; k. Tf_2O, DIPEA, DMAP, CH_2Cl_2; l. $H_2C{=}C(OEt)SnBu_3$, $Pd(OAc)_2$, dppp, Et_3N, DMF, 60 to 70 °C; m. NBS, THF, H_2O, 0 °C; n. *N-tert*-butoxycarbonyl-S-*p*-methoxybenzyl-L-cysteine-thioamide, EtOH.

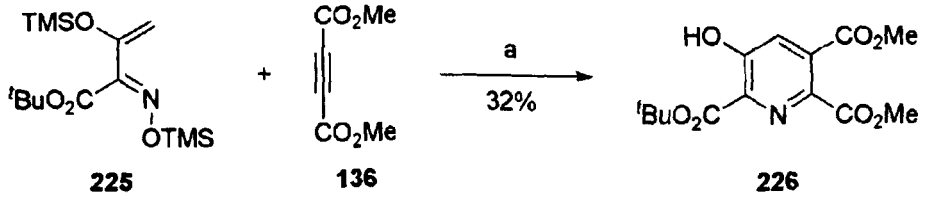
Moody and coworkers have recently reported a different approach based on the ozonolysis of quinoline **223**, readily prepared from acetanilide **221** using a double Vilsmeier reaction followed by Baeyer-Villiger oxidation. Ozonolysis of the benzene ring revealed the orthogonally protected pyridine **224** suitable for further elaboration (**Scheme 56**).[82]



Scheme 56. *Reagents and conditions*: a. $POCl_3$, DMF, 0 °C then 120 °C; b. $MeCO_3H$, $CHCl_3$; c. $KHCO_3$, MeOH (aq.); d. Ac_2O, K_2CO_3, DMF, 50 °C; e. O_3, CH_2Cl_2, -20 °C then Me_2S, -20 °C to rt.

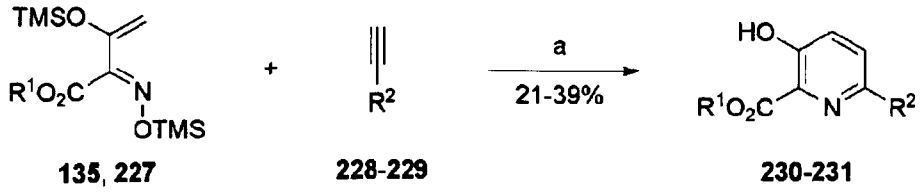
2.2 Background Work on Intermolecular Hetero-Diels-Alder Reactions

Previous work in this laboratory focused on the reaction of *bis*-trimethylsilyl protected dienes such as **225** with a range of dienophiles.[83] Thus, cycloaddition of 1-aza-1,3-butadiene **225** with DMAD **136** was carried out under reflux in toluene to afford the corresponding 3-hydroxypyridine **226** in moderate yield (**Scheme 57**) after 14 days.[54] The poor yields may be explained by hydrolysis of the labile silyl enol ether moiety in the diene under the reaction conditions prior to cycloaddition.



Scheme 57. *Reagents and conditions*: a. toluene, reflux, 14 d.

The reactivity of these 1-azadienes with unsymmetrical dienophiles was also assessed, including methyl propiolate **228** (R^2 = CO_2Me) and 3-butyn-2-one **229** (R^2 = COMe), both of which react with complete regioselectivity to afford the 2,3,6-trisubstituted pyridines **230-231** in poor to moderate yield (**Scheme 58, Table 22**).[83]



Scheme 58. *Reagents and conditions*: a. toluene, 120 °C, sealed tube, 20 h-4 d.

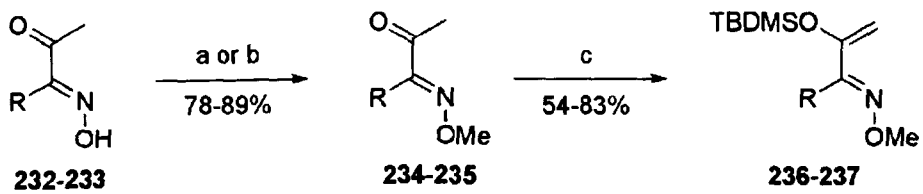
Table 22. Diels-Alder reactions of 1-azadienes **135** and **227** with unsymmetrical dienophiles.

Entry	1-Azadiene	R^1	Dienophile	R^2	Product	Yield/%
1	**135**	Me	**228**	CO_2Me	**230**	21
2	**227**	Bn	**229**	COMe	**231**	39

The application of microwave irradiation has been shown to accelerate the rate of many organic reactions.[84, 85] Indeed, several examples of hetero-Diels-Alder reactions have been reported under microwave conditions, including both 1- and 2-azadienes.[21, 55, 86-88] Therefore at the start of this project it was envisaged that the long reaction times previously observed might be reduced by performing the reaction under these conditions. In order to address the issue of the poor yields observed, the use of a more hydrolytically stable silicon-based protecting group was also investigated.

2.3 Synthesis and Cycloadditions of α,β-Unsaturated Oximes

A range of 3-*tert*-butyldimethylsiloxy-α,β-unsaturated oximes was prepared, and their reactivity in the intermolecular hetero-Diels-Alder reaction investigated. Thus, *O*-methyl oximes **236-237** were prepared from the free oximes **232-233**[89] in two steps via *O*-alkylation[90] and formation of the *tert*-butyldimethylsilyl enol ether on treatment with TBDMS triflate and DIPEA (**Scheme 59**, **Table 23**).[50]



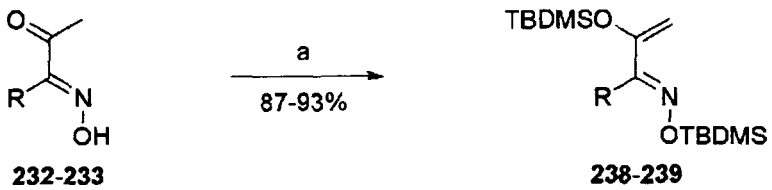
232-233 **234-235** **236-237**

Scheme 59. *Reagents and conditions*: a. 10% NaOH (aq.), Me_2SO_4, rt 30 min then reflux 5 min; b. K_2CO_3, Me_2SO_4, acetone, 4 °C, 24 h; c. TBDMSOTf, DIPEA, CH_2Cl_2, 0 °C, 3 h.

Table 23. Synthesis of 3-siloxy-1-aza-1,3-butadienes **236-237**.

Entry	α-ketoxime	R	*O*-Methyl Oxime	Yield/%	1-Azadiene	Yield/%
1	**232**	Me	**234**	78	**236**	83
2	**233**	CO_2Me	**235**	89	**237**	54

The analogous TBDMS oxime derivatives **238-239** were also prepared in high yield from the free oximes **232-233** in a single step on treatment with TBDMS triflate and DIPEA (**Scheme 60**).[50]



232-233 **238-239**

Scheme 60. *Reagents and conditions*: a. TBDMSOTf, DIPEA, CH_2Cl_2, 0 °C, 5-18 h.

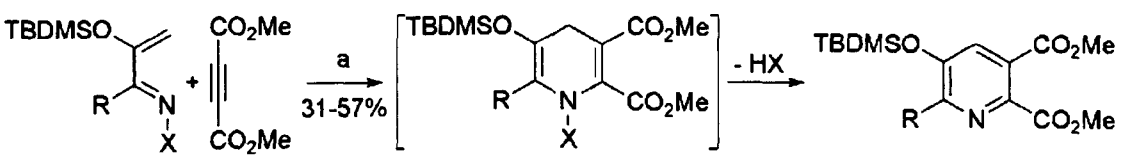
Table 24. Synthesis of 3-siloxy-1-aza-1,3-butadienes **238-239**.

Entry	α-Ketoxime	R	1Azadiene	Yield/%
1	**232**	Me	**238**	87
2	**233**	CO_2Me	**239**	93

The intermolecular hetero-Diels-Alder reactions of 3-siloxy-1-azadienes **236-237** and **238-239** were next investigated. Unfortunately, only traces of the expected pyridines was observed on heating *O*-methyl oxime ethers **236-237** with DMAD **136** at 150 °C under microwave heating, as well as significant decomposition of the starting materials (**Table 25**, entries 1-2). This result mirrors those of Gilchrist[29] and Boger,[9] who have also found *O*-alkyl oxime ethers to be unreactive in certain hetero-Diels-Alder reactions. One possible reason for this is that the *O*-methyl oximes **236-237** are not sufficiently electron-rich to interact with electron-deficient dienophiles due to an unfavourable $HOMO_{diene}$-$LUMO_{dienophile}$ energy separation.

However, treatment of the more electron-rich **238** and **239** with either 1 or 2 equivalents of DMAD **136** in a sealed tube at 150 °C under microwave irradiation proceeded smoothly to afford the protected pyridines **240-241** in moderate yields after cycloaddition and concomitant loss of *tert*-butyldimethylsilanol in only a few hours (**Table 25**, entries 4, 6, 8). The primary dihydro-pyridine cycloadducts were not observed under the reaction conditions. As may be expected, introduction of the

electron-withdrawing ester moiety at C-2 of the diene lowered its reactivity towards the electron-deficient dienophile, leading to slightly longer reaction time and lower yield (**Table 25**, entry 8). Increasing the temperature to 180 °C shortened the reaction time even further (**Table 25**, entries 5, 7, 9, 10). A control reaction performed in a sealed tube at 150 °C gave the expected pyridine **240** in 57% yield after 6 hours (**Table 25**, entry 3). However, the use of microwave irradiation remains a safe, clean, and efficient means of performing high temperature reactions and was used in the following studies on hydrazone derived 1-azadienes.



236-239 **136** **240-241**

Scheme 61. *Reagents and conditions*: a. toluene or toluene/THF, Δ, MW.

Table 25. Cycloaddition of α,β-unsaturated oximes **238-239** with DMAD **136** under microwave heating.[a]

Entry	1-Azadiene	R	X	DMAD (equiv.)	Temp. /°C	Time /h	Product	Yield /%[b]
1	**236**	Me	OMe	2.0	150	2	**240**	-
2	**237**	CO_2Me	OMe	2.0	150	0.5	**241**	-
3[c]	**238**	Me	OTBDMS	2.0	150	6	**240**	57
4	**238**	Me	OTBDMS	2.0	150	6	**240**	56
5	**238**	Me	OTBDMS	2.0	180	2	**240**	56
6	**238**	Me	OTBDMS	1.0	150	8	**240**	50
7	**238**	Me	OTBDMS	1.0	180	3	**240**	50
8	**239**	CO_2Me	OTBDMS	2.0	150	10	**241**	32
9	**239**	CO_2Me	OTBDMS	2.0	180	6	**241**	31
10	**239**	CO_2Me	OTBDMS	1.0	180	8	**241**	45

[a] reactions were carried out in a CEM Discover™ microwave reactor.

[b] isolated yield after chromatography on silica gel.

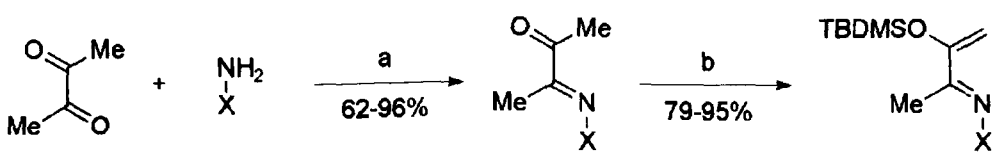
[c] reaction carried out in a sealed tube under standard thermal heating.

2.4 Synthesis and Cycloadditions of α,β-Unsaturated Hydrazones

As discussed above, the most commonly used 1-azadienes in hetero-Diels-Alder reactions are the *N,N*-dimethylhydrazones,[2-8] as they are generally considered to be more electron-rich than their equivalent oximes due to the increased electron donation of the dimethylamino group compared to the alkoxy or siloxy group. Thus, α,β-unsaturated hydrazones exhibit greater reactivity towards highly electron-deficient dienophiles such as DMAD **136** based on the likely frontier orbital interactions ($HOMO_{diene}/LUMO_{dienophile}$), assuming that a normal electron-demand cycloaddition is in operation. A number of reactions of α,β-unsaturated hydrazones with electron-

deficient alkenes and benzoquinones as dienophiles have therefore been reported.[2, 4, 8] Reactions with alkynes however are less common. The C-3 oxygenated hydrazones are also known, although no Diels-Alder reactions of these dienes with alkynes have been reported.

A series of 3-siloxy-α,β-unsaturated hydrazones was therefore prepared in order to probe the reactivity of these 1-azadienes towards electron-deficient acetylenes (**Scheme 62**). The required α-ketohydrazones **248-252** were prepared by condensation of 2,3-butanedione **242** with the appropriate hydrazines **243-247**. Although **243-244** and **247** are commercially available, 1-*tert*-butoxycarbonyl- and 1-benzyloxycarbonyl-1-methyl-hydrazines **245** and **246** had to be synthesised by protection of methylhydrazine with di-*tert*-butyl dicarbonate[91] and benzyl chloroformate[92] in 92% and 58% yield respectively. Silyl enol ether formation was achieved under standard conditions in excellent yield (**Table 26**, entries 1-2, 4-5), except for *N*-*tert*-butoxycarbonylhydrazone **250**, which suffered loss of the protecting group under the reaction conditions (**Table 26**, entry 4).[50]



242 **243-247** **248-252** **53** **253-256**

Scheme 62. *Reagents and conditions*: a. EtOH, 0 °C, 16 h; b. TBDMSOTf, DIPEA, CH_2Cl_2, 0 °C, 5-18 h.

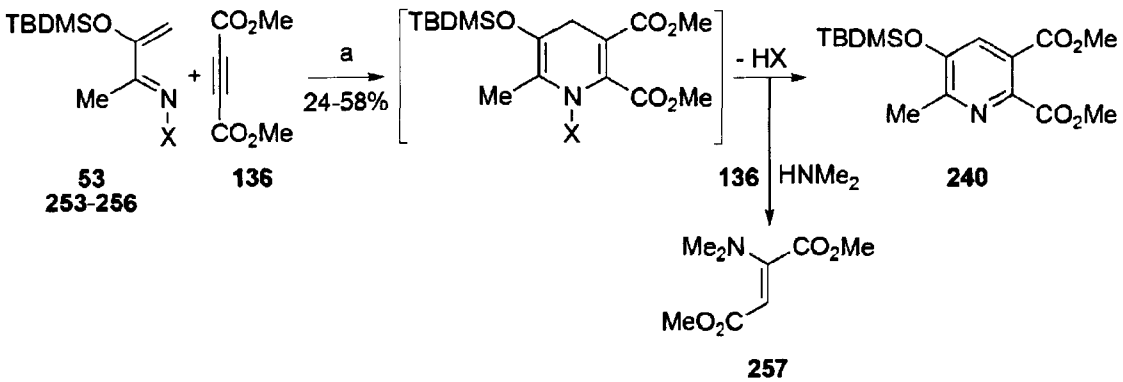
Table 26. Synthesis of 3-siloxy-α,β-unsaturated hydrazones **53** and **253-256**.

Entry	Hydrazine	X	α-keto-hydrazone	Yield/%	1-Azadiene	Yield/%
1	**243**	NMe_2	**248**	72	**53**	95
2	**244**	piperidinyl	**249**	62	**253**	84
3	**245**	NMeBoc	**250**	96	**254**	-
4	**246**	NMeCbz	**251**	78	**255**	93
5	**247**	phthalimido	**252**	87	**256**	79

Initial work on the hydrazone series focused on the cycloaddition of known 3-*tert*-butyldimethylsiloxy-2-methyl-1-aza-1,3-butadiene **53**[50] with DMAD **136** (**Scheme 63**). In a control experiment, treatment of **53** with **136** gave the desired cycloadduct **240** in 53% yield after 20 hours under reflux in toluene (**Table 27**, entry 1). Again, no evidence of the primary cycloadduct was detected. Once again the use of microwave irradiation was investigated in an attempt to decrease the reaction time and improve the yield.

Irradiation of equimolar amounts of 1-azadiene **53** and DMAD **136** at 150 °C in toluene in a sealed tube for 2 hours afforded the desired pyridine **240**, still protected as the TBDMS ether and in poor yield, due to the competing formation of the conjugate addition product dimethyl 2-(dimethylamino)fumarate **257**, caused by reaction between the dienophile and dimethylamine liberated upon aromatisation of the initial Diels-Alder adduct (**Table 27**, entry 2). Thus, 2 equivalents of the dienophile were necessary to achieve complete consumption of the 1-azadiene, allowing the product to be isolated in comparable yield to the thermal reaction in only 2 hours (**Table 27**, entry 3). Once again, increasing the temperature to 180 °C shortened the reaction time even further (**Table 27**, entry 4). A control reaction performed in a sealed tube at 150

°C under thermal conditions gave the anticipated pyridine **240** in 46% yield after 2 hours.



Scheme 63. *Reagents and conditions*: a. toluene or toluene/THF, Δ, MW.

Table 27. Cycloaddition of α,β-unsaturated hydrazones **53** and **253-256** with DMAD **136** under microwave heating.[a]

Entry	1-Azadiene	X	Temp./°C	Time/h	Yield/%[b]
1[c]	**53**	NMe_2	110	20	53
2[d]	**53**	NMe_2	150	2	24
3	**53**	NMe_2	150	2	52
4	**53**	NMe_2	180	0.75	44
5	**253**	piperidinyl	150	2	47
6	**255**	NMeCbz	150	4	46
7	**256**	phthalimido	180	3	58
8[d]	**256**	phthalimido	180	4	54

[a] reactions were carried out in a CEM Discover™ microwave reactor using 2 equivalents of DMAD **136**.

[b] isolated yield after chromatography on silica gel.

[c] reaction carried out under reflux in toluene.

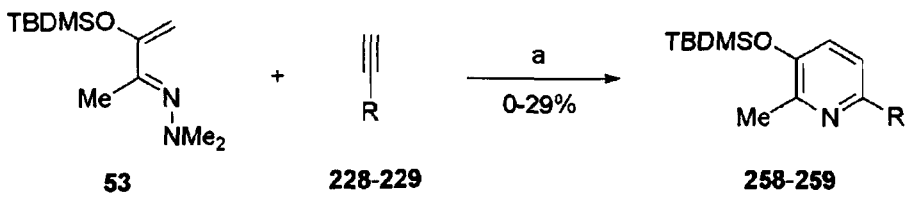
[d] 1 equiv. of DMAD **136** used.

It was envisaged that by altering the nature of the leaving group in the aromatisation step it would be possible to limit the formation of the competing Michael adducts, and so improve the yield of the desired product.

As may be expected, the piperidinyl derivative **253** displayed similar reactivity to **53** (**Table 27**, entry 5), including the formation of unwanted conjugate addition product **257**. Introduction of a single electron-withdrawing substituent onto the leaving group in 1-azadiene **255** also failed to prevent by-product formation (**Table 27**, entry 6). However, the introduction of a second electron-withdrawing group onto hydrazone **256**, derived from *N*-aminophthalimide,[93] completely suppressed Michael addition of the nitrogen leaving group into the dienophile, leading to an increased yield, although higher temperature was necessary to effect the cyclisation (**Table 27**, entry 7). Only a single equivalent of DMAD **136** was therefore required with this diene (**Table 27**, entry 8).

The reactivity of unsymmetrical dienophiles, in particular methyl propiolate **228** and 3-butyn-2-one **229**, was also investigated. The most reactive 1-azadiene **53** was chosen for this study as longer reaction times were expected as less electron-deficient (and hence less reactive) dienophiles were being employed (**Scheme 64**). Indeed, increasing the reaction temperature to 180 °C for 6 hours was necessary to achieve complete consumption of the 1-azadiene (**Table 28**, entries 1-2). Poor yields of a single regioisomer were obtained in each case, as assigned by ^{1}H NMR spectroscopy based on the coupling constants (8.3 Hz) between the two *ortho* aromatic protons. Other unsymmetrical dienophiles such as 4-phenyl-3-butyn-2-one, 4-trimethylsilanyloxy-but-2-ynoic acid ethyl ester and methyl trimethylsilylpropiolate were examined and

found to be unreactive under the reaction conditions, presumably due to steric as well as electronic considerations.



53 **228-229** **258-259**

Scheme 64. *Reagents and conditions*: a. toluene/THF, Δ, MW.

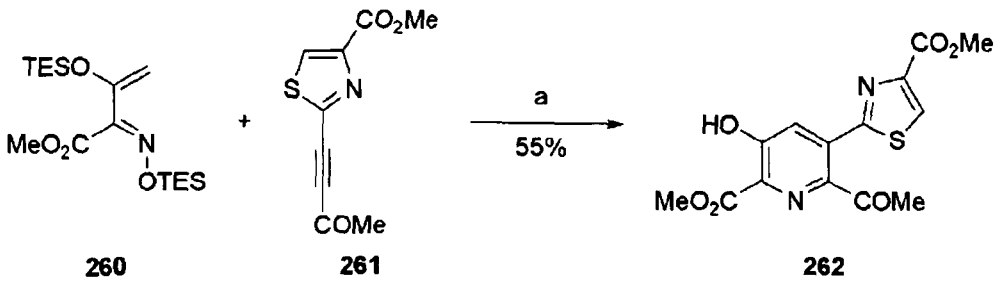
Table 28. Cycloaddition of **53** with unsymmetrical acetylenes **228-229** under microwave heating.[a]

Entry	Dienophile	R	Temp./°C	Time/h	Product	Yield/%[b]
1	**228**	CO_2Me	180	6	**258**	29
2	**229**	COMe	180	6	**259**	28

[a] reactions were carried out in a CEM Discover™ microwave reactor (300 W) with simultaneous cooling using 2 equivalents of dienophile.

[b] isolated yield after chromatography on silica gel.

This methodology has very recently been extended by Arndt and coworkers, who utilised a hetero-Diels-Alder reaction as the key step in their synthesis of the pyridine core of nosiheptide **214** (**Scheme 65**).[94]



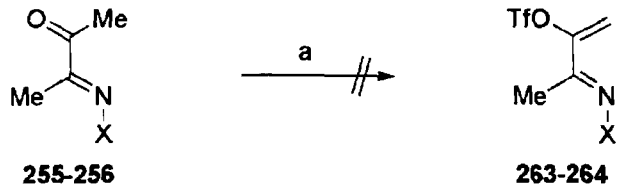
260 **261** **262**

Scheme 65. *Reagents and conditions*: a. toluene, 180 °C.

2.5 Attempted Synthesis of Vinyl Triflates as 1-Azadienes

Synthesis of 1-azadienes bearing a triflate group at the C-3 position would allow direct formation of highly-substituted pyridines bearing a leaving group suitable for further elaboration by transition-metal catalysed cross-coupling reactions. Two hydrazones were chosen for this study, namely *N*-methyl-*N*-Cbz protected hydrazone **255** and phthalimido derivative **256**, as they both bear electron-withdrawing substituents on the hydrazone which should prevent substitution of the triflate group by the amine liberated in the aromatisation step through a competing S_NAr process.

Attempted formation of the vinyl triflates from hydrazones **255** and **256** was carried out under a range of conditions (**Scheme 66**). Initially, trifluoromethanesulfonic anhydride was used as the electrophile, but *N*-phenylbis(trifluoromethane)sulfonimide was chosen for the bulk of the study due to ease of handling of the reagent. A range of bases and solvents were also screened, as well as the addition of DMPU as a co-solvent. However all reactions failed to give any of the desired product, and this work was therefore abandoned.



255-256 **263-264**

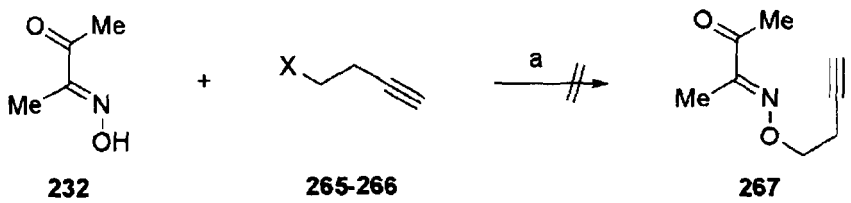
Scheme 66. *Reagents and conditions*: a. see table.

Table 29. Attempted synthesis of vinyl triflates and nonaflates

Entry	Hydrazone	X	Conditions	Product	Result
1	**255**	NMeCbz	Tf_2O, DIPEA, CH_2Cl_2	**263**	SM
2	**255**	NMeCbz	Tf_2O, Et_3N, CH_2Cl_2	**263**	SM
3	**255**	NMeCbz	$PhNTf_2$, DIPEA, CH_2Cl_2	**263**	SM
4	**255**	NMeCbz	$PhNTf_2$, KHMDS, THF	**263**	decomp.
5	**256**	phthalimido	$PhNTf_2$, DIPEA, CH_2Cl_2	**264**	SM
6	**256**	phthalimido	$PhNTf_2$, Et_3N, CH_2Cl_2	**264**	SM
7	**256**	phthalimido	$PhNTf_2$, NaH, THF	**264**	trace
8	**256**	phthalimido	$PhNTf_2$, Cs_2CO_3, THF	**264**	SM
9	**256**	phthalimido	$PhNTf_2$, KHMDS, THF	**264**	SM
10	**256**	phthalimido	$PhNTf_2$, *n*-BuLI, THF	**264**	decomp.
11	**256**	phthalimido	$PhNTf_2$, LiHMDS DMPU, THF	**264**	decomp.
12	**256**	phthalimido	$PhNTf_2$, NaH DMPU, THF	**264**	trace

2.6 Attempted Synthesis of Intramolecular Substrates

A brief study on the synthesis of intramolecular hetero-Diels-Alder substrates was also undertaken. First, alkylation of 2,3-butanedione monoxime **232** was attempted using a variety of bases with either tosylate[95] **265** or iodide[96] **266** as the electrophile (**Scheme 67, Table 30**). Unfortunately, recovery of the starting materials or decomposition was observed in all cases.



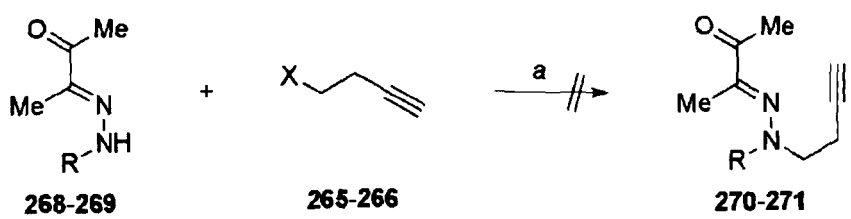
232 **265-266** **267**

Scheme 67. *Reagents and conditions*: a. see table.

Table 30.

Entry	Electrophile	X	Conditions	Result
1	**265**	OTs	10% NaOH (aq.)	SM
2	**265**	OTs	NaH, THF	SM
3	**266**	I	10% NaOH (aq.)	SM
4	**266**	I	*n*-BuLi, THF	decomp.

Next, hydrazones **268**[97] and **269** were prepared from 2,3-butanedione **232** via condensation with the appropriate hydrazine.[98] Alkylation of the hydrazone nitrogen was then examined under a range of conditions (**Scheme 68, Table 31**), though once again none of the desired product was obtained.



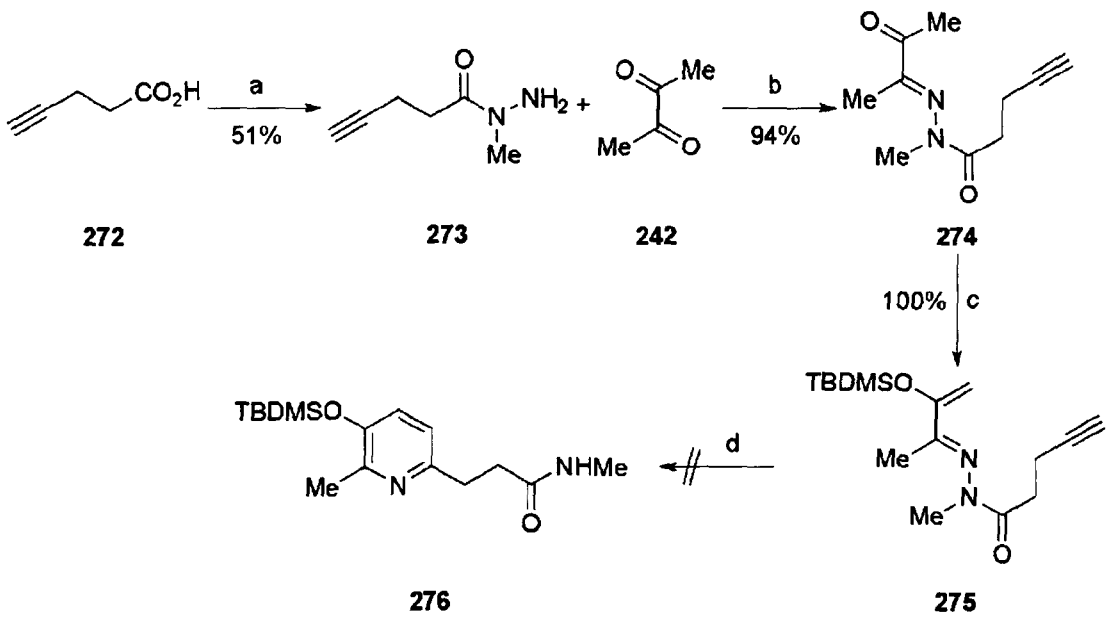
268-269 **265-266** **270-271**

Scheme 68. *Reagents and conditions*: a. see table.

Table 31. Attempted alkylation of hydrazones **268-269**.

Entry	Hydrazone	R	Electrophile	X	Conditions	Product	Result
1	**268**	Me	**265**	OTs	Cs_2CO_3, acetone	**270**	SM
2	**268**	Me	**266**	I	Cs_2CO_3, acetone	**270**	SM
3	**268**	Me	**266**	I	*n*-BuLi, THF	**270**	SM
4	**269**	Cbz	**266**	I	K_2CO_3, EtOAc	**271**	SM
5	**269**	Cbz	**266**	I	NaH, DMF	**271**	SM
6	**269**	Cbz	**266**	I	*n*-BuLi, THF	**271**	SM

Finally, incorporation of the side-chain onto the nitrogen atom prior to formation of the hydrazone was attempted. Thus, following procedures reported by Gilchrist and coworkers, pent-4-ynoic acid **272** was converted to hydrazide **273** via the acid chloride and treatment with methyl hydrazine (**Scheme 69**).[29] Reaction of 2,3-butanedione **242** with hydrazide **273** and subsequent formation of the silyl enol ether delivered the IMDA substrate **275**. Intramolecular cycloaddition was attempted under microwave heating, but after 10 hours at 180 °C only decomposition of the starting material was observed. This work was therefore abandoned.



Scheme 69. *Reagents and conditions*: a. $SOCl_2$, reflux, 45 min, then $MeNHNH_2$, CH_2Cl_2, 0 °C, 1 h; b. EtOH, 0 °C, 3.75 h then rt, 18 h; c. TBDMSOTf, DIPEA, CH_2Cl_2, 0 °C, 18 h; d. toluene/THF, 180 °C, MW.

2.7 Conclusions

Series of α,β-unsaturated oximes and hydrazones have been prepared, and their reactivity in the hetero-Diels-Alder cycloaddition with electron-deficient acetylenes evaluated. In general, the bis-silylated oximes proved to be less reactive than the corresponding hydrazones, requiring much longer reaction times to obtain complete consumption of the starting materials. This is due to the superior electron donation of the dimethylamino substituent into the diene, thereby further raising the energy of the HOMO of the diene. However, as described in the next chapter, in the intramolecular mode, oxime containing dienes do participate in hetero-Diels-Alder reactions with appropriate dienophiles.

Changing the electronic properties of the *N*-1 substituent has a strong effect on the reactivity of the α,β-unsaturated hydrazones. The stronger the electron-donating group, the more reactive the 1-azadiene, and the shorter the reaction time observed for Diels-Alder cycloaddition. However, side-products were observed due to addition of the nucleophilic amine liberated after aromatisation into the starting materials. Introducing electron-withdrawing groups onto the hydrazone nitrogen lowered the reactivity of the 1-azadiene, leading to longer reaction times for cycloaddition, though suppression of the unwanted side-reactions was obtained.

The synthesis of 1-azadienes bearing a triflate group at the 3-position was attempted. A variety of reaction conditions were screened, but this work was unsuccessful. An intramolecular hetero-Diels-Alder substrate was also constructed, although cycloaddition could not be achieved under microwave heating.

Chapter 3

Results and Discussion

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Towards the Formal Synthesis of Streptonigrin

3.1 Introduction

Streptonigrin[99] **215** was first isolated by Rao and Cullen[100] in 1959 from *Streptomyces flocculus* and was shown to exhibit activity against several animal tumours.[101-105] Streptonigrin **215** has also been isolated from other *Streptomyces* strains, namely *S. rufochromogenes* and *S. echinatus*,[106] as well as from *Actinomyces albus var. bruneomycini* (**Figure 7**).[107, 108] Two further closely related antibiotics streptonigrone[109] **277** and lavendamycin **278** have since been isolated.[110, 111] Lavendamycin **278** has also been postulated as a possible biosynthetic precursor to streptonigrin **215** and related analogues.

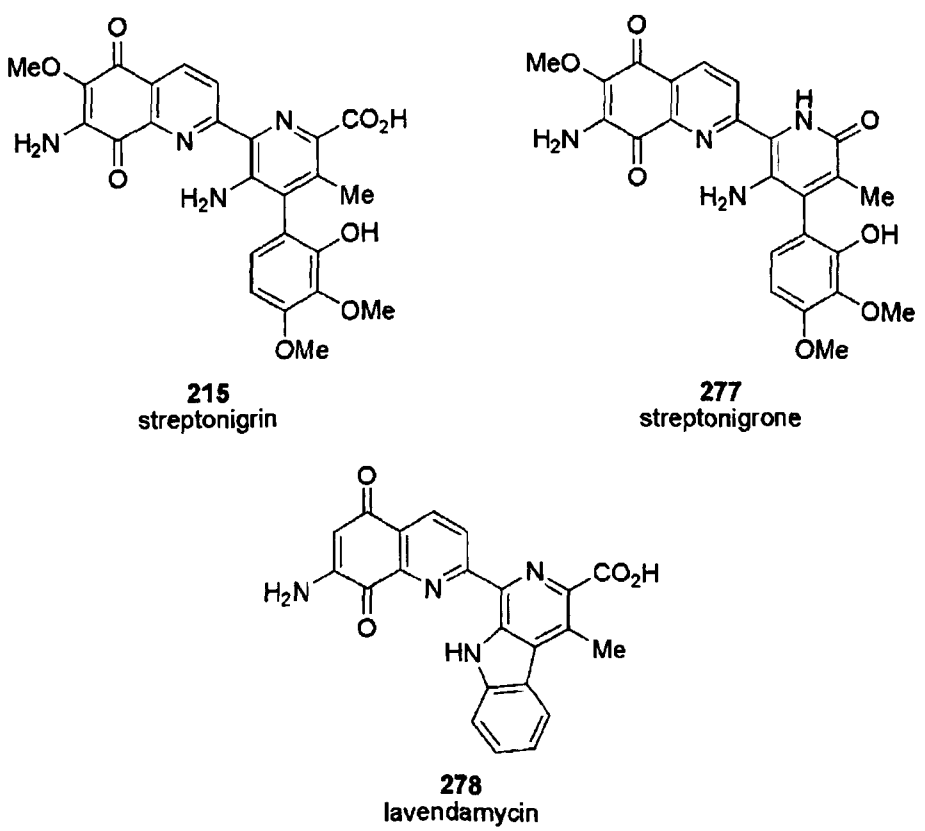


Figure 7.

The structure of streponigrin **215** was first reported by Woodward and coworkers in 1963 on the basis of spectroscopic and degradative studies.[112] Further evidence for this structure was reported in 1975 by Chiu and Lipscomb through X-ray diffraction analysis.[113] More recent NMR studies by Lown and Begleiter,[114] and Harding and coworkers[115, 116] have confirmed the structure as **215**.

The AB- and C-rings of **215** are held coplanar due to an internal hydrogen bond between the pyridine amino group and the quinoline nitrogen (**Figure 8**).[113] Streptonigrin **215** is also optically active due to hindered rotation about the CD-biaryl bond. Although initially assigned as the *P*-isomer by Dholakia and Gillard,[117] subsequent work by Tennent and Rickards[118] suggested that streptonigrin **215** adopts the *M*-configuration. More recent work by Bringmann and coworkers has confirmed that the *M*-isomer is indeed the correct structure.[119]

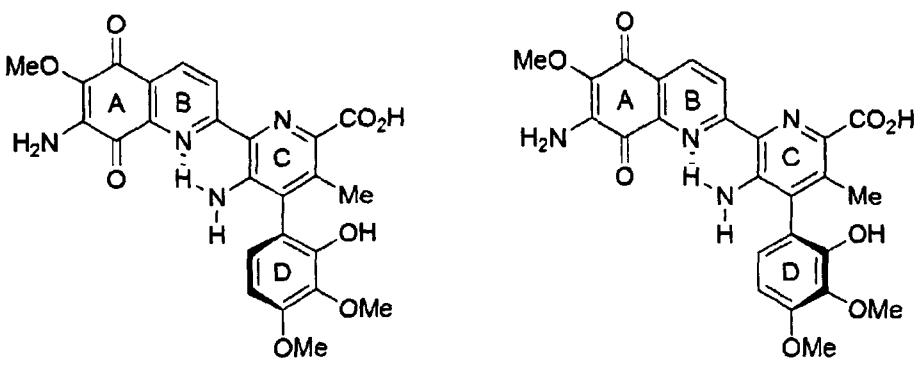


Figure 8.

3.2 Biological Activity of Streptonigrin

Streptonigrin **215** has been shown to exhibit potent antiviral activity against both Gram-positive and Gram-negative bacteria, as well as strong antitumour activity towards a range of both animal and human cancer cell lines. However, clinical use has been precluded due to severe side effects including prolonged bone marrow depression.

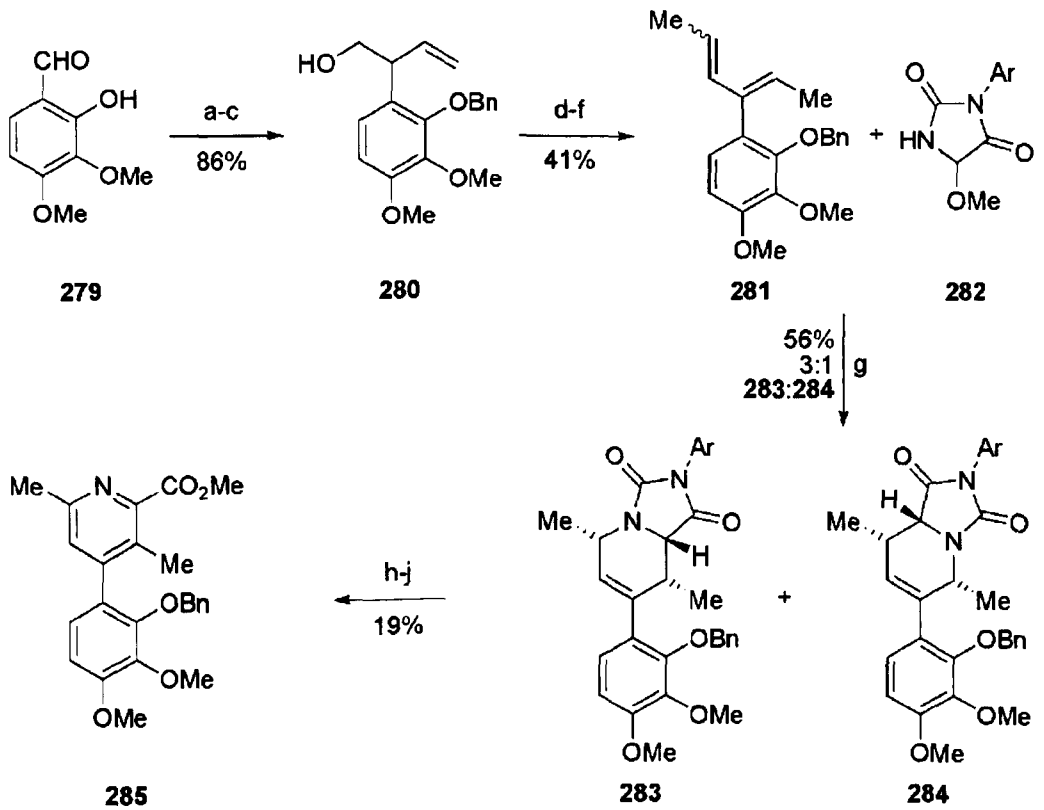
The mechanism of action for the anticancer activity of streptonigrin **215** has been the source of much interest. It has been shown to inhibit DNA and RNA synthesis and cause DNA strand breaks *in vitro* and *in vivo*, as well as promote mammalian topoisomerase II-induced cell death. Streptonigrin **215** binds irreversibly to DNA in the presence of certain metal ions, in particular zinc and copper, followed by reduction of the quinone moiety by either a one- or two-electron process to the hydroquinone or semiquinone radical. Hydrogen peroxide (formed from the superoxide radical via a superoxide dismutase (SOD) catalysed process) then induces oxidation back to the quinone and formation of hydroxyl radicals, leading to its DNA damaging effects.

Due to its unique structural properties and potent biological activity, it is unsurprising that streptonigrin **215** has provided much inspiration to the synthetic chemist. Indeed, considerable effort has been made to prepare analogues of streptonigrin that maintain the high degrees of biological activity displayed by the natural product yet lack the toxic side effects.

3.3 Previous Syntheses of Streptonigrin

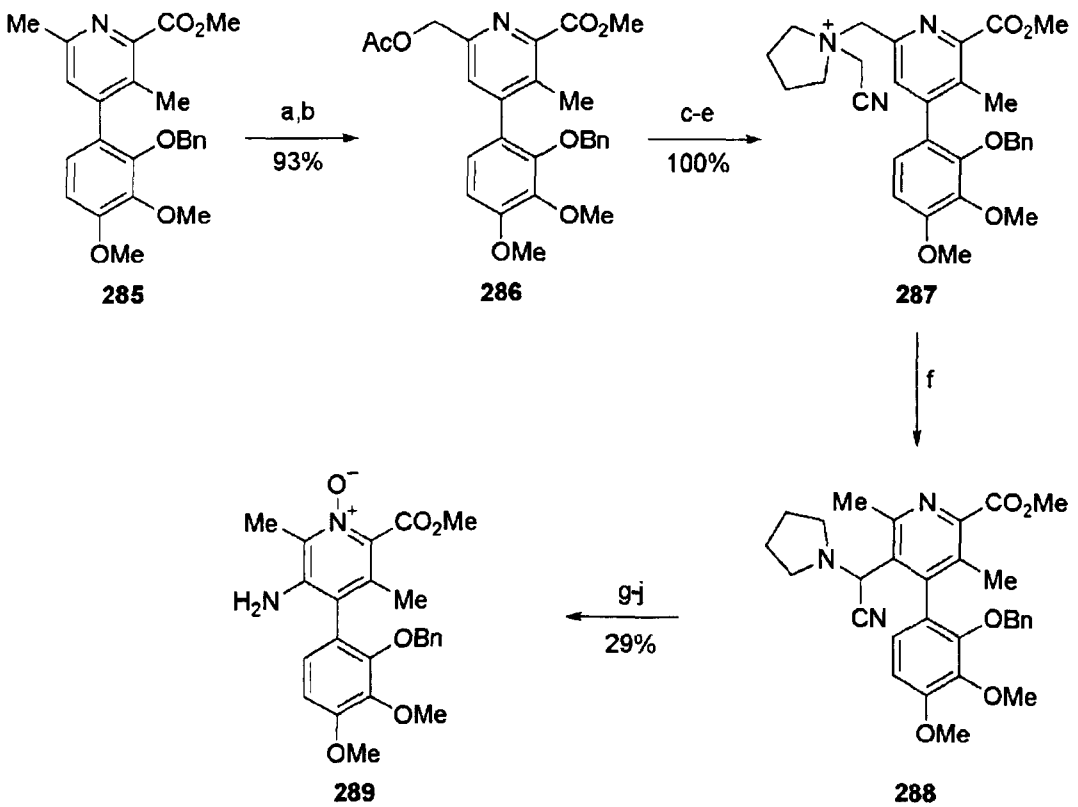
Three previous total syntheses of streptonigrin **215** have been reported. The first was presented by Weinreb and coworkers[120-122] in 1980, followed closely by Kende[123-125] in 1981 and Boger in 1985.[126-128]

Weinreb's approach was centred on two key reactions; an imino-Diels-Alder reaction for the formation of the CD-ring fragment, followed by a modified Friedländer reaction to install the quinoline ring. Weinreb's synthesis started with readily available aldehyde **279**, which was converted into the homoallylic alcohol **280** in three steps (**Scheme 70**). Oxidation to the aldehyde and Wittig reaction gave the desired diene fragment **281**. A Diels-Alder reaction with a dienophile formed *in situ* from hydantoin **282** proceeded smoothly to afford a 3:1 mixture of regioisomeric products **283** and **284** in favour of the desired isomer. The mixture was not separated at this stage but converted into the key pyridine intermediate **285** in a further three steps.



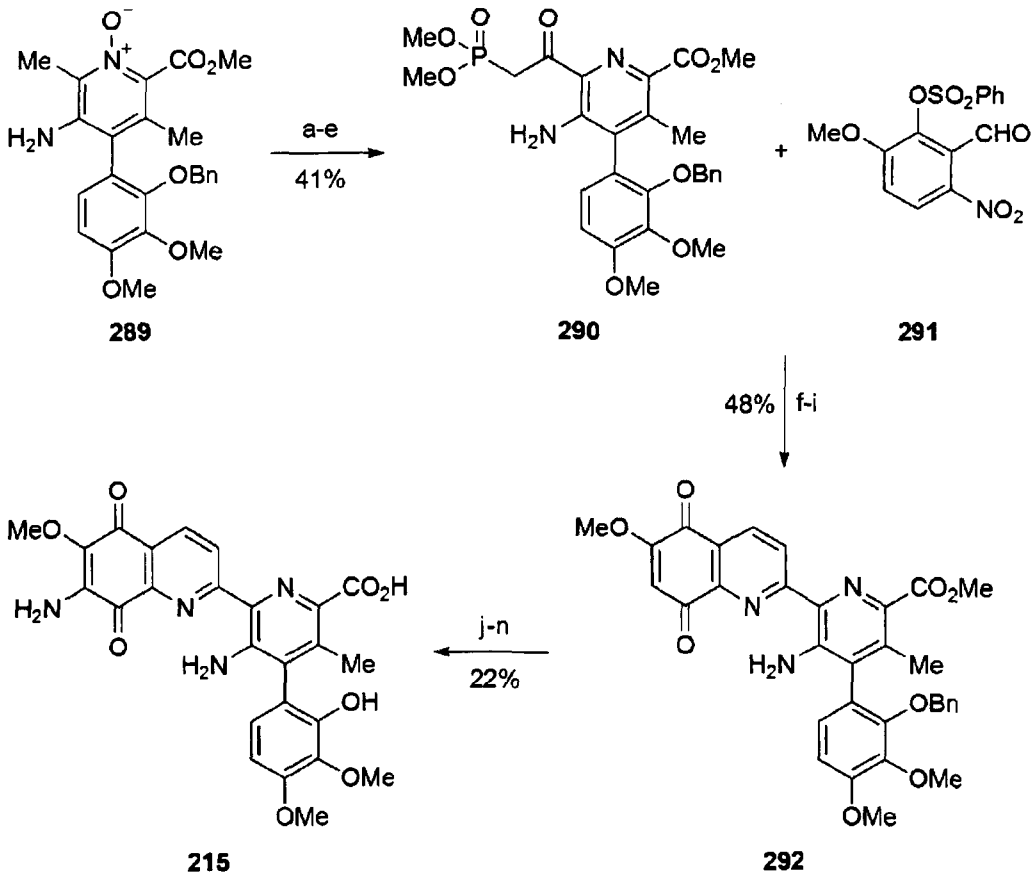
Scheme 70. *Reagents and conditions*: a. BnBr, K_2CO_3, glyme; b. $Me_3S^+I^-$, NaH, DMSO; c. H_2C=CHMgBr, THF; d. CrO_3, py, CH_2Cl_2; e. 5% HCl (aq.); f. Ph_3PCHMe, *n*-BuLi, KO^{t}Bu; g. xylene, reflux; h. $Ba(OH)_2$, 1,4-dioxane, H_2O; i. $SOCl_2$, MeOH; j. Pd/C, toluene; k. *m*-CPBA, CH_2Cl_2.

Installation of the remaining amino substituent into the C-5 position of the pyridine was accomplished in a further ten steps (**Scheme 71**). Key transformations included the Polonovski-type *N*-oxide rearrangement (**285** to **286**), a further [2,3]-sigmatropic shift to functionalise C-5 (**287** to **288**) and the Yamada modification of the Curtius rearrangement to give the desired aminopyridine (**288** to **289**).



Scheme 71. *Reagents and conditions*: a. *m*-CPBA, CH_2Cl_2; b. Ac_2O, 120 °C; c. K_2CO_3, MeOH; d. $SOCl_2$, benzene; e. *N*-(cyanomethyl)pyrrolidine, DMSO; f. KO^{t}Bu, THF, DMSO; g. $(CO_2H)_2$, THF, H_2O; h. TFPAA, Na_2HPO_4, CH_2Cl_2; i. $KMnO_4$, acetone, H_2O; j. $(PhO)_2PON_3$, benzene, H_2O.

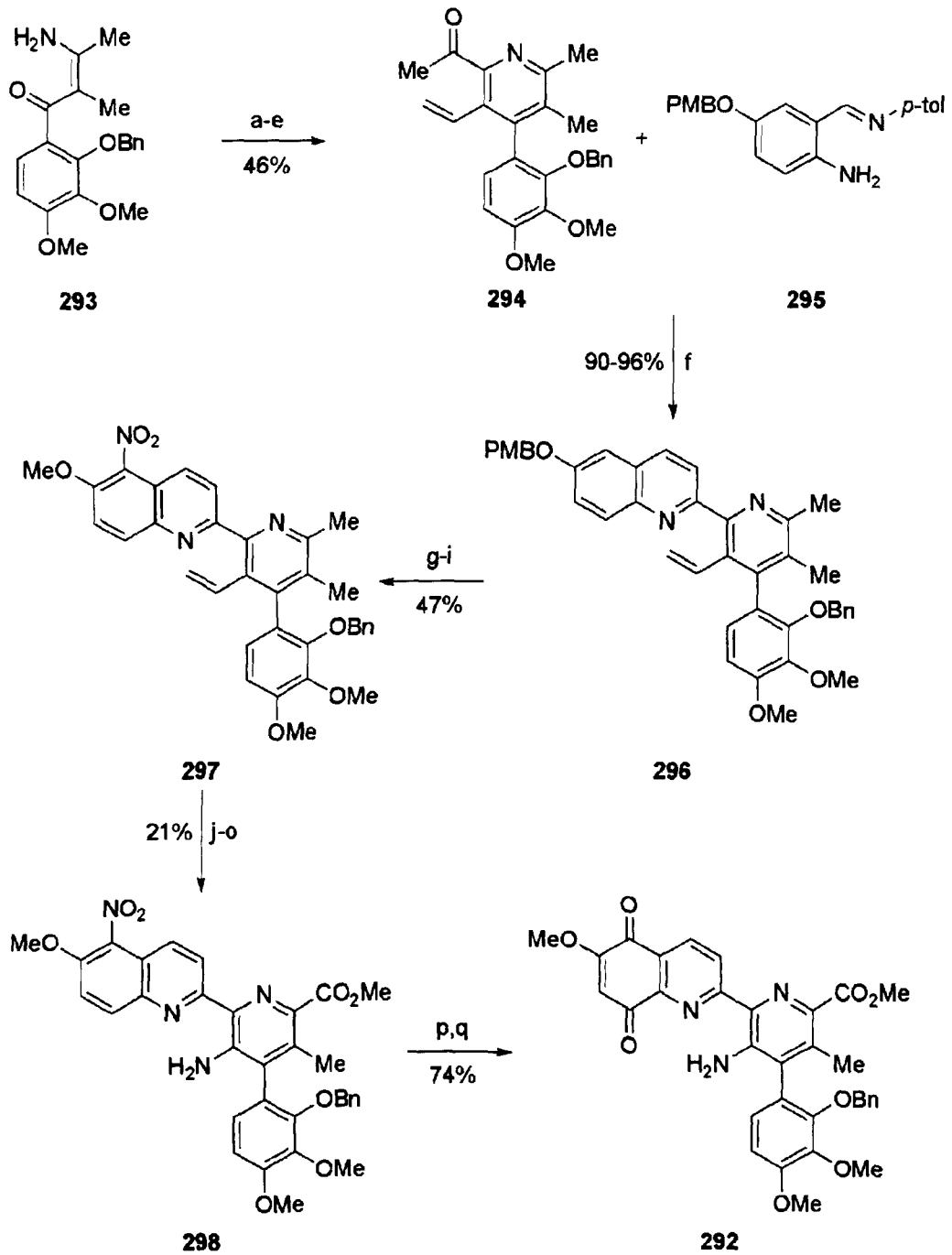
A second Polonovski-type rearrangement was then carried out, followed by oxidation, formation of the *β*-ketophosphonate **290** and Wadsworth-Emmons reaction with known aldehyde **291** to afford the nitrochalcone (**Scheme 72**). Reduction and cyclisation proceeded smoothly, followed by deprotection and oxidation to the quinone **292**, which was converted into streptonigrin **215** following standard procedures. In total, the natural product was prepared in over 30 steps in 0.034% overall yield from readily available starting materials.



Scheme 72. *Reagents and conditions*: a. Ac_2O, 120 °C; b. K_2CO_3, MeOH; c. MnO_2, $CHCl_3$; d. *n*-BuLi, $(MeO)_2POMe$, THF; e. MnO_2, $CHCl_3$; f. KH, benzene; g. $Na_2S_2O_4$, MeOH, H_2O; h. NaOMe, MeOH; i. Fremy's salt, KH_2PO_4 (aq.), MeOH; j. NaN_3, ICl, MeCN; k. NaN_3, THF; l. $Na_2S_2O_4$, MeOH, H_2O; m. $AlCl_3$, $CHCl_3$; n. K_2CO_3, MeOH, H_2O.

Kende's approach to streptonigrin **215** also featured a Friedländer condensation to assemble the quinoline fragment. The synthesis started from the known ketoenamine **293**, which was condensed with methyl acetoacetate to afford the pyridone. Reduction of the C-3 acetyl group to the secondary alcohol proceeded smoothly on treatment with sodium borohydride. Chlorination and dehydration to the vinyl group was achieved using phenylphosphoryl dichloride, followed by heating for 3 hours. Treatment with copper cyanide and addition of methylmagnesium bromide gave the key vinylpyridine **294** (**Scheme 73**).

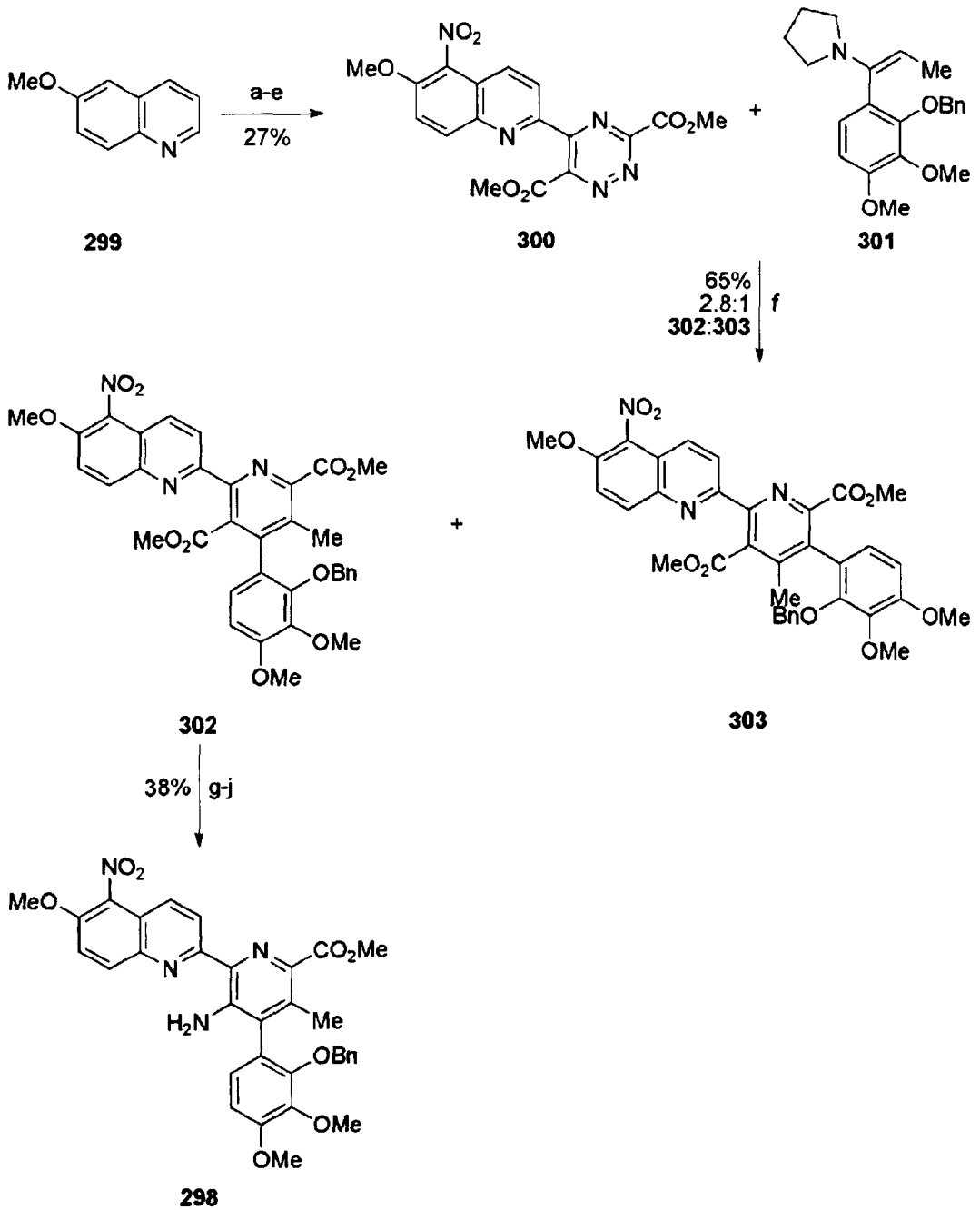
A Friedländer condensation was then carried out between **294** and iminoaniline **295** using potassium *tert*-butoxide in *tert*-butanol to give the tetracyclic compound **296**. Deprotection, nitration and methylation of the phenol gave **297**. The vinyl unit was then cleaved under oxidative conditions to install the carboxylic acid, and oxidation of the methyl group adjacent to the pyridine nitrogen was achieved with selenium dioxide, followed by sodium chlorite. Selective esterification of the less hindered acid and a modified Curtius rearrangement afforded intermediate **298**. Reduction of the nitro group and oxidation to the quinone gave advanced intermediate **292**, which had previously been prepared by Weinreb. Synthesis of this compound therefore constituted a formal total synthesis of streptonigrin **215**. The clever use of the vinyl unit as a masking group for the amino group shortened the synthesis considerably when compared to Weinreb's, allowing the natural product to be obtained in 22 steps and in 0.069% overall yield.



Scheme 73. *Reagents and conditions*: a. methyl acetoacetate, xylene, reflux; b. $NaBH_4$, THF, IPA; c. $PhPOCl_2$; d. CuCN, DMF, reflux; e. MeMgBr, benzene; f. KO^{t}Bu, toluene, ^{t}BuOH; g. TFA; h. HNO_3, $MeNO_2$; i. Me_2SO_4, K_2CO_3, acetone, reflux; j. OsO_4, NMO, acetone, ^{t}BuOH, H_2O; k. $NaIO_4$, 1,4-dioxane, H_2O, 80 °C; l. SeO_2, AcOH, reflux; m. $NaClO_2$, H_2NSO_3H, NaOAc, dioxane, H_2O; n. MeOH, AcCl; o. $(PhO)_2PON_3$, Et_3N, benzene, H_2O; p. $Na_2S_2O_4$, THF, MeOH, H_2O, reflux; q. Fremy's salt, Na_2HPO_4, acetone, H_2O.

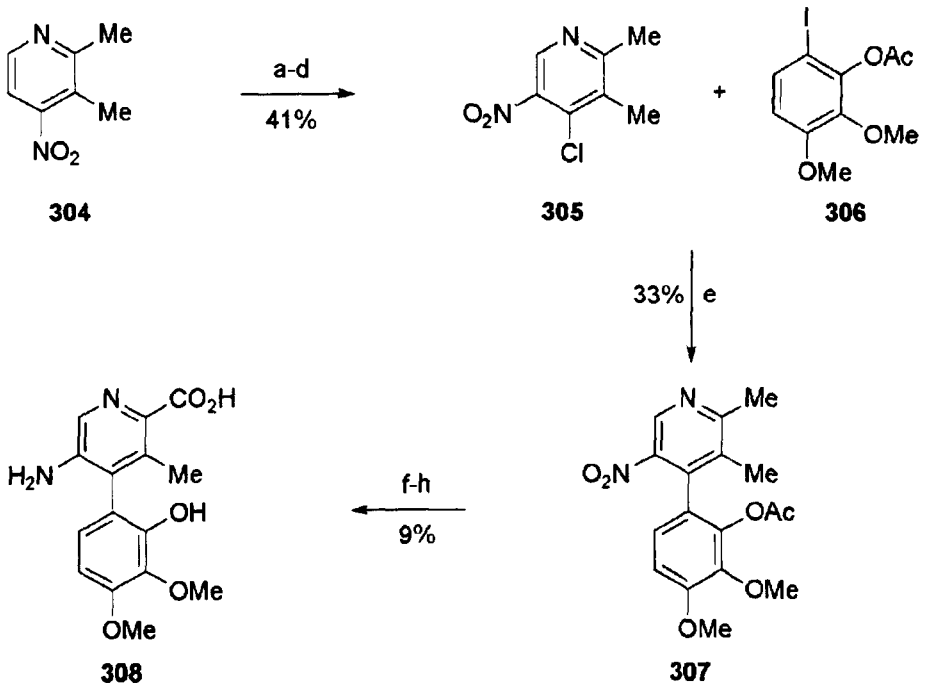
Boger and coworkers have also reported a formal synthesis of streptonigrin **215**. The key steps involved two sequential inverse electron-demand hetero-Diels-Alder reactions, with concomitant loss of nitrogen in each case. The starting material for this synthesis was 6-methoxyquinoline **299**, which was first converted into 2-cyano-6-methoxyquinoline, followed by nitration and formation of the thioamide using hydrogen sulfide in diethylamine (**Scheme 74**). Treatment of the thioamide with iodomethane gave the desired *S*-methylthioimidate, which underwent hetero-Diels-Alder reaction with 1,2,4,5-tetrazine-3,6-dicarboxylate, followed by extrusion of nitrogen, to deliver the desired triazine **300**.

A further hetero-Diels-Alder reaction with enamine **301** gave a 2.8:1 mixture of the regioisomers **302** and **303**. The desired isomer **302** was hydrolysed to the diacid with the sodium salt of phenylselenol, which unfortunately also effected *O*-demethylation of the aromatic ether. Selective esterification, modified Curtius rearrangement and re-methylation of the phenolic hydroxyl group afforded the advanced intermediate **298** which could be converted into streptonigrin **215** using the methodology previously described by Weinreb and Kende. This synthesis has proved to be the most efficient, comprising a total of 13 steps from readily available starting materials and in 1.8% overall yield.



Scheme 74. *Reagents and conditions*: a.TsCl, KCN, CH_2Cl_2, H_2O; b. HNO_3, H_2SO_4; c. H_2S, Et_2NH, 1,4-dioxane; d. MeI, MeCN; e. dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate, 1,4-dioxane, 80 °C; f. CH_2Cl_2, 6.2 kbar; g. NaSePh, THF-HMPA, 70 °C; h. HCl, MeOH, H_2O; i. $(PhO)_2PON_3$, benzene, H_2O; j. MeI, K_2CO_3, THF.

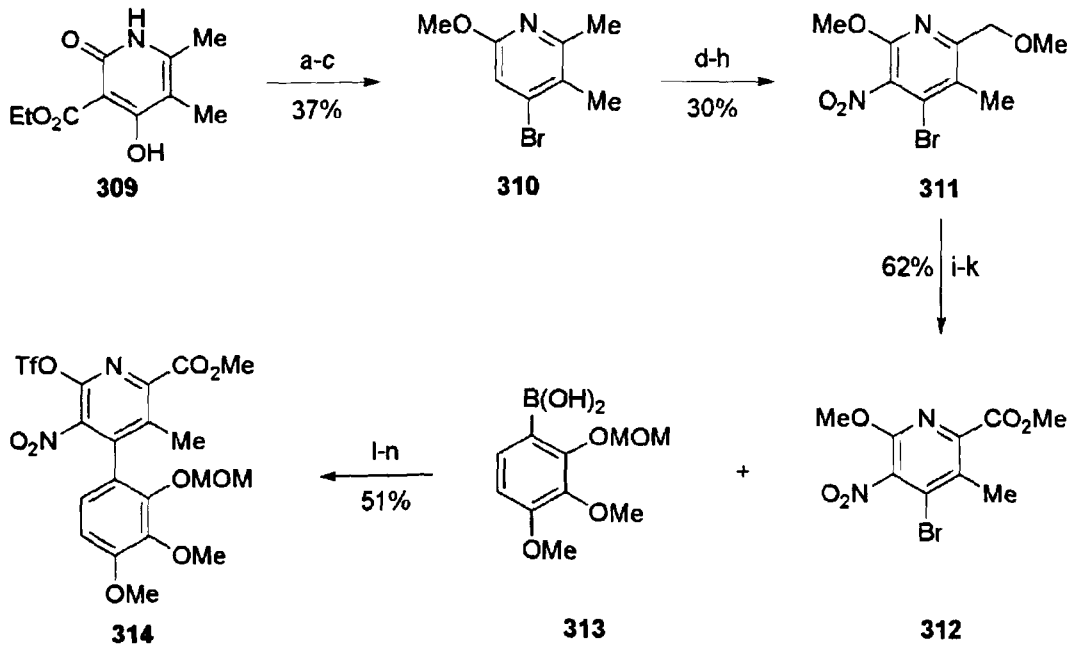
Three syntheses of the CD-rings of streptonigrin **215** have also been reported. The first was reported by Cheng and coworkers in 1976 in stepwise fashion starting from pyrogallol.[129] Cheng later reported a more convergent synthesis based on an unsymmetrical Ullmann reaction.[130] Thus, known 2,3-dimethyl-4-nitropyridine **304** was first converted into 4-chloro-2,3-dimethyl-5-nitropyridine **305** in 4 steps (**Scheme 75**). The second partner **306** for biaryl cross-coupling was prepared from 2,3-dimethoxyphenol by protection of the free hydroxyl group and iodination. The key unsymmetrical Ullmann coupling was carried out in 33% yield using copper dust in DMF at 140 °C to deliver **307**. Oxidation of the pyridine methyl group to the carboxylic acid was carried out in 2 steps on treatment with selenium dioxide under reflux in dioxane followed by silver oxide in basic aqueous ethanol. Hydrolysis of the acetate protecting group was also effected under the reaction conditions. Final reduction of the nitro group was carried out under catalytic hydrogenolysis to afford the streptonigrin CD-rings **308**.



Scheme 75. *Reagents and conditions*: a. KOAc, Ac_2O, reflux, 16 h; b. H_2O, reflux, 4 h; c. HNO_3, H_2SO_4, 65 °C, 2 h; $POCl_3$, PCl_5, reflux, 2 h; e. copper dust, DMF, 140 °C, 90 min; f. SeO_2, dioxane, reflux, 3 h; g. Ag_2O, NaOH, EtOH, H_2O, 10 °C, 20 min then NaOH, 40 °C, 2 h; h. H_2, 5% Pd/C, MeOH, 3 h.

The third CD-ring synthesis of streptonigrin **215** was presented by DeShong and coworkers, also based on a biaryl cross-coupling strategy.[131] The synthesis started from known pyridone **309**, which was converted into bromopyridine **310** after hydrolysis, decarboxylation, treatment with phosphorus oxybromide and methylation (**Scheme 76**). Formation of the *N*-oxide, Polonovski rearrangement and subsequent hydrolysis of the acetate, methylation and nitration delivered **311**. DeShong found that oxidation at the C-2 position of the pyridine to the carboxylate ester was crucial before biaryl cross coupling, as the same transformation could not be achieved with the D-ring in place. Thus, removal of the methyl group from **311** was effected using boron trichloride in quantitative yield, followed by oxidation and esterification to give **312**. Suzuki cross-coupling with boronic acid **313** was accomplished in 68% yield.

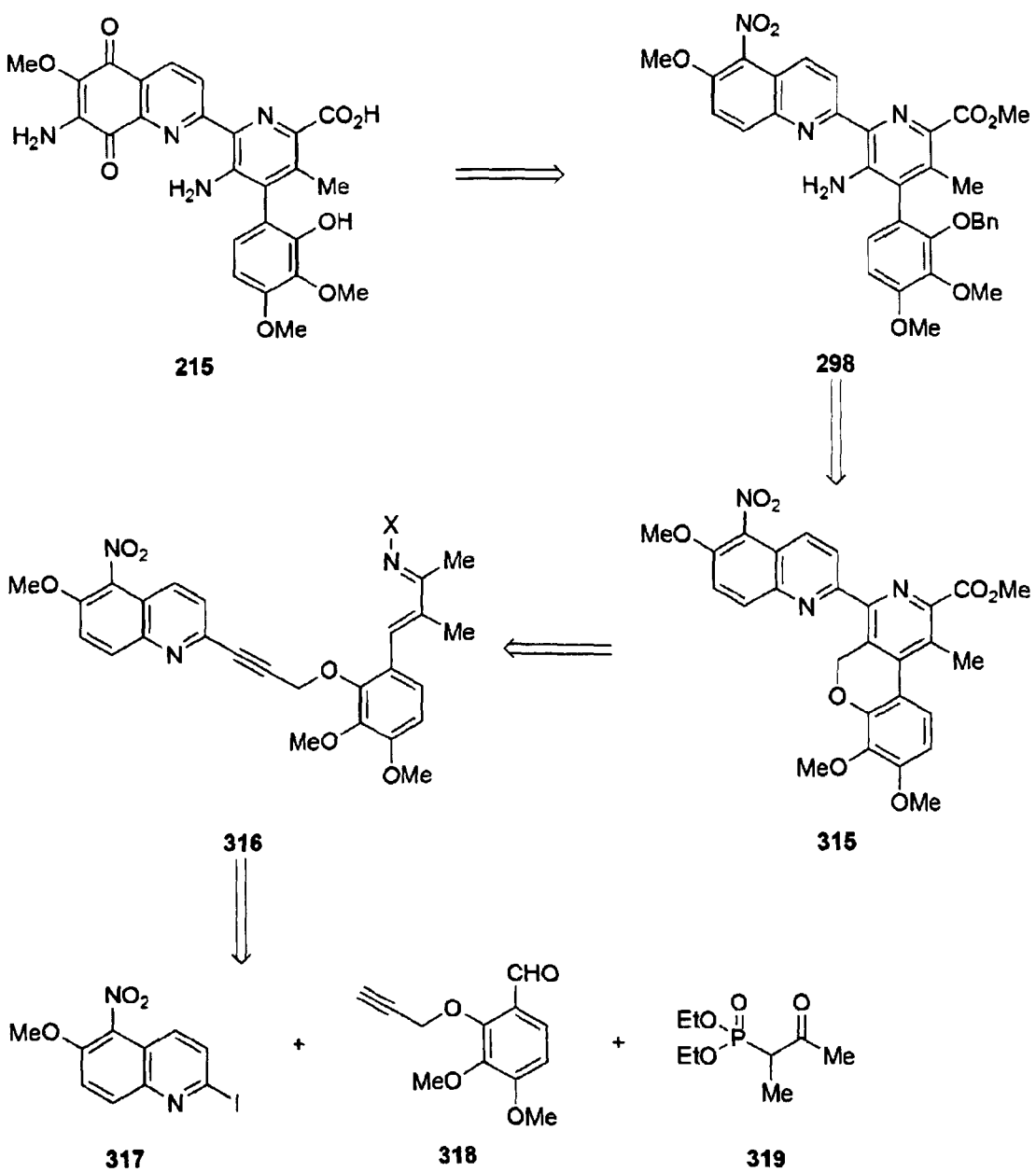
Treatment of the biaryl product with phosphorus tribromide revealed the pyridone, which was converted into the corresponding pyridyl triflate **314**. A second biaryl cross-coupling of **314** with an AB-ring precursor has yet to be achieved.



Scheme 76. *Reagents and conditions*: a. 2 M NaOH, reflux, 2 h then HCl, rt, 12 h; b. $POBr_3$, DMF, 110 °C, 45 min; c. MeI, Ag_2CO_3, $CHCl_3$, 50 °C, 24 h; d. 30% H_2O_2, AcOH, 60 °C, 3 d; e. Ac_2O, 120 °C, 2 h; f. K_2CO_3, MeOH; g. Ag_2O, MeI, THF, reflux, 4 d; h. HNO_3, H_2SO_4, rt, 2 d; i. BCl_3, CH_2Cl_2, 0 °C to rt, 16 h; j. $KMnO_4$, NaOH, H_2O, rt, 24 h; k. H_2SO_4, MeOH, reflux, 16 h; l. $Pd(PPh_3)_4$, CsF, DME, 75 °C, 24 h; m. PBr_3, DCE, reflux, 12 h; n. Tf_2O, DMAP, CH_2Cl_2, 0 °C to rt, 12 h.

3.4 Retrosynthetic Analysis

Our current retrosynthetic analysis of streptonigrin **215** begins with a change in oxidation levels and functional group transformations which lead to the advanced intermediate **298** previously obtained by Kende and Boger (**Scheme 77**). The synthesis of this compound will therefore constitute a formal total synthesis of streptonigrin **215**.



Scheme 77.

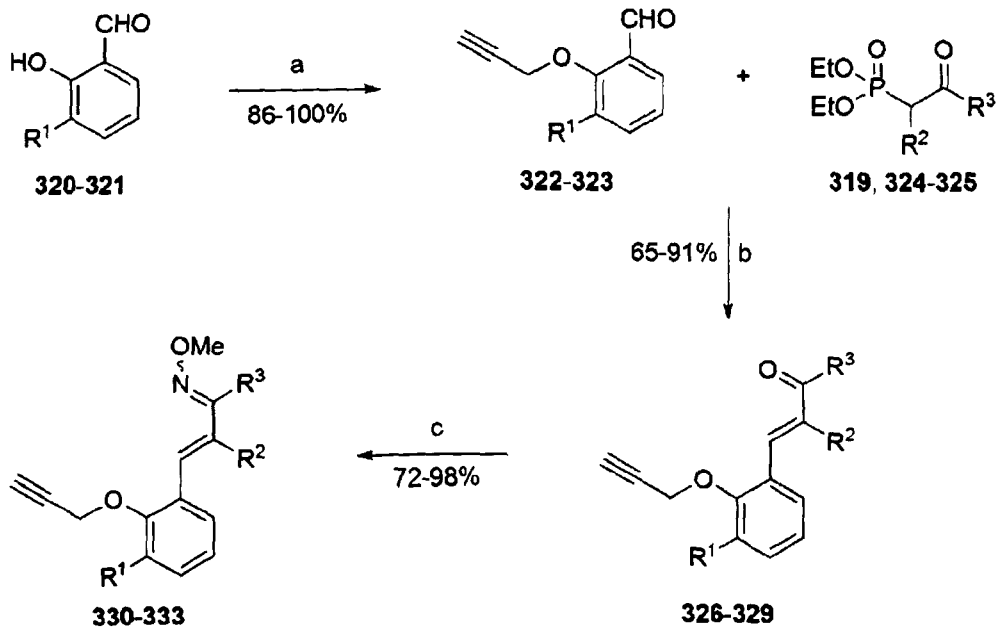
Compound **298** is anticipated to arise from the cyclic ether **315** via oxidation of the pyran ring to the lactone, followed by hydrolysis, protection of the phenol and Curtius rearrangement. Disconnection of the pyridine ring of **315** reveals **316** as a likely precursor. In the forward sense an intramolecular hetero-Diels-Alder reaction between the acetylene and 1-azadiene units followed by selective oxidation of the pyridine C-2 methyl group will generate the desired heterocycle. Rapid construction of IMDA substrate **316** was expected from AB-ring precursor **317**, D-ring **318** and phosphonate **319** through Sonogashira cross-coupling and Wadsworth-Emmons reaction.

3.5 Model Intramolecular Hetero-Diels-Alder Reactions

In order to ascertain whether an intramolecular hetero-Diels-Alder route was a viable strategy for the synthesis of the pyridine core of streptonigrin **215**, a series of model systems were prepared and their IMDA cycloadditions evaluated.[132]

The required substrates for hetero-Diels-Alder reaction were prepared in three steps from commercially available starting materials. First, alkylation of salicylaldehyde **320** and 3-methylsalicylaldehyde **321** with propargyl chloride proceeded in excellent yield to provide the aryl propargyl ethers **322-323** (**Scheme 78**, **Table 32**).[59] Next, the Wadsworth-Emmons reaction was examined. Treatment of the required β-ketophosphonates **319** and **324-325**, obtained either from commercial sources or by acylation of the phosphonate-derived carbanion by known or modified procedures,[133] with sodium hydride or potassium *tert*-butoxide in 1,2-dimethoxyethane (DME) or toluene, followed by addition of the aldehyde gave the desired α,β-unsaturated ketones **326-329** as single (*E*)-geometric isomers in good to excellent yields.

Treatment of related α,β-unsaturated ketones (*vide infra*) with *N,N*-dimethylhydrazine led to a complex mixture of products due to the competing formation of Michael adducts. Thus, further functionalisation to the 1-aza-1,3-butadiene moiety was readily achieved by conversion of **326-329** into the *O*-methyl oximes **330-333** on heating with methoxylamine hydrochloride and sodium acetate trihydrate in aqueous ethanol in almost quantitative yield, without the need for further purification by column chromatography.

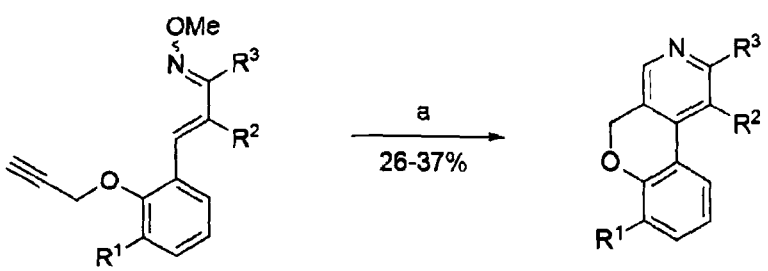


Scheme 78. *Reagents and conditions*: a. $HC{\equiv}CCH_2Cl$, K_2CO_3, EtOH, reflux, 16 h; b. $(RO)_2P(O)CHR^2COR^3$, NaH or KO^{t}Bu, DME or toluene, rt, 16 h; c. $MeONH_2{\cdot}HCl$, $NaOAc{\cdot}3H_2O$, EtOH, H_2O, 60 °C, 16 h.

Table 32. Synthesis of IMDA substrates **330-333**.

Entry	Phenol	R^1	R^2	R^3	Ketone	Yield/%	Oxime	Yield/%
1	**320**	H	H	Me	**326**	91	**330**	98
2	**321**	Me	H	Me	**327**	76	**331**	98
3	**321**	Me	Me	Me	**328**	71	**332**	72
4	**321**	Me	Me	CH_2OMe	**329**	65	**333**	95

The key IMDA cycloadditions were then examined under simple heating (**Scheme 79**). Thus, heating oxime **330** to 180 °C in xylene in a sealed tube gave the desired [*c*]-annelated pyridine **334** in 30% yield after 16 h (**Table 33**, entry 1). A minor byproduct was isolated in 8% yield, which was identified as (3*E*)-4-(2*H*-chromen-8-yl)but-3-en-2-one *O*-methyloxime **338**, that presumably arises through a [3,3]-sigmatropic rearrangement and [1,5]-hydrogen shift in analogous fashion to that previously reported for vinyl hydrazone dienes (**Scheme 80**).[59]



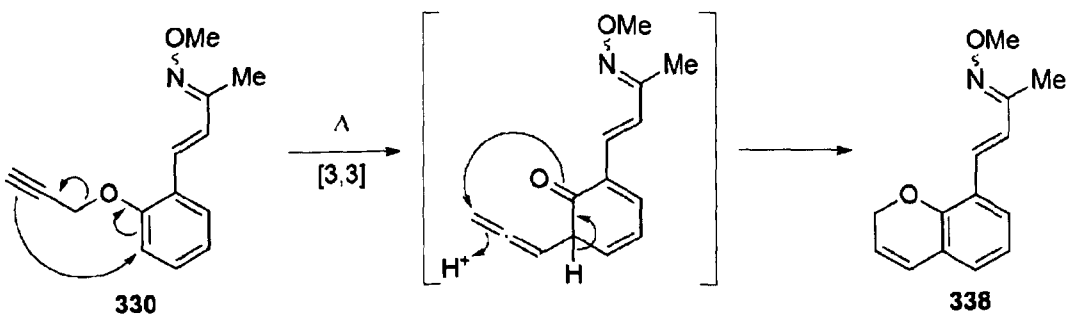
330-333 **334-337**

Scheme 79. *Reagents and conditions*: a. xylene, 180 °C, sealed tube, 16 h.

Table 33. IMDA cycloaddition of α,β-unsaturated *O*-methyl oximes **330-333**.

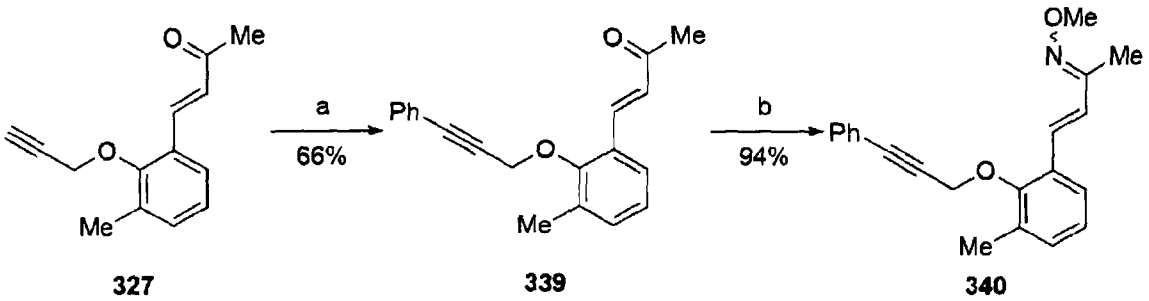
Entry	IMDA Substrate	R^1	R^2	R^3	Product	Yield/%
1	**330**	H	H	Me	**334**	30
2	**331**	Me	H	Me	**335**	37
3	**332**	Me	Me	Me	**336**	26
4	**333**	Me	Me	CH_2OMe	**337**	27

A blocking substituent in the form of a methyl group *ortho* to the propargylic ether moiety eliminates this competing rearrangement, and the desired pyridine **335** was isolated in 37% yield (**Table 33**, entry 2). Variations in the diene component were also tolerated. Indeed, IMDA reaction of substrates **332-333** (**Table 33**, entries 3-4) proceeded smoothly, albeit in modest yield, to provide the tetra-substituted pyridines **336-337**.



Scheme 80. Formation of chromene byproduct **338** resulting from competing [3,3]-sigmatropic rearrangement of **330**.

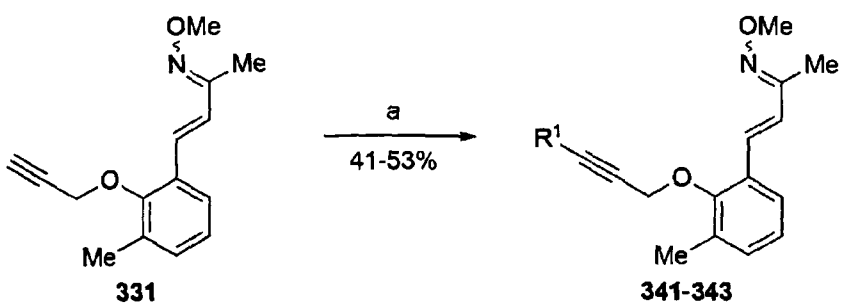
A range of substrates bearing a substituent at the terminus of the acetylenic dienophile were also prepared in order to examine their effect on the intramolecular hetero-Diels-Alder reaction. The IMDA substrate **340** was obtained by Sonogashira reaction between acetylene **327** and iodobenzene under standard conditions[134] to give **339**, followed by formation of the corresponding oxime as detailed above (**Scheme 81**).



327 339 340

Scheme 81. *Reagents and conditions*: a. PhI, $Pd(PPh_3)_2Cl_2$ (7 mol%), CuI, Et_3N, THF, 60 °C, 16 h.; b. $MeONH_2 \cdot HCl$, $NaOAc \cdot 3H_2O$, EtOH, H_2O, 60 °C, 16 h.

IMDA substrates **341-343** bearing a methyl ester, chloro or trimethylsilyl group at the alkyne terminus were prepared directly from oxime **331** via deprotonation of the acidic acetylenic proton with lithium hexamethyldisilazide (LiHMDS) and trapping with the appropriate electrophile (**Scheme 82**).[135-137]



331 341-343

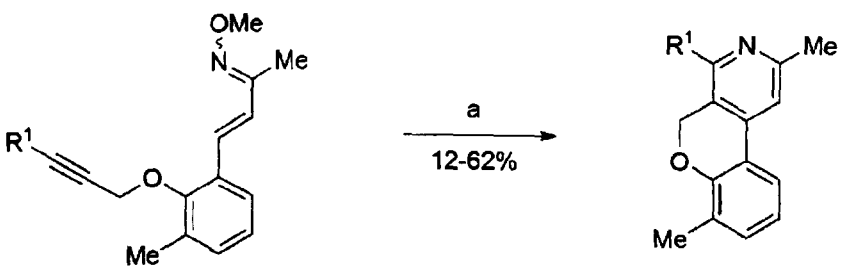
Scheme 82. *Reagents and conditions*: a. LiHMDS, electrophile, THF, -78 °C to rt, 16 h.

Table 34. Functionalisation of terminal acetylene **331**.

Entry	Electrophile	R^1	Product	Yield/%
1	$ClCO_2Me$	CO_2Me	**341**	41
2	NCS	Cl	**342**	49
3	TMSCl	TMS	**343**	53

Once again, the key IMDA reactions were investigated under simple thermal heating. Introduction of an electron-withdrawing group at the terminus of the acetylene would be expected to facilitate the IMDA reaction on the basis of lowering the relevant LUMO of the dienophile, assuming that the α,β-unsaturated oximes participate in a normal electron-demand hetero-Diels-Alder reaction ($HOMO_{diene}/LUMO_{dienophile}$).

This indeed proved to be the case (**Scheme 83**); heating oxime **340** in xylene in a sealed tube at 180 °C gave the desired tetra-substituted pyridine **344** in 62% yield (**Table 35**, entry 1). The reaction still proceeded at 140 °C, unlike the terminal acetylenes, although a slight drop in yield was noticed (**Table 35**, entry 2). IMDA reaction of oxime **341** also proceeded smoothly, with the expected product **345** isolated in 50% and 41% yield after 16 h at 180 °C and 140 °C respectively (**Table 35**, entries 3-4).



340-343 **335** **344-346**

Scheme 83. *Reagents and conditions*: a. xylene, 140-180 °C, sealed tube, 16 h.

Table 35. IMDA reactions of α,β-unsaturated oximes **340-343**.

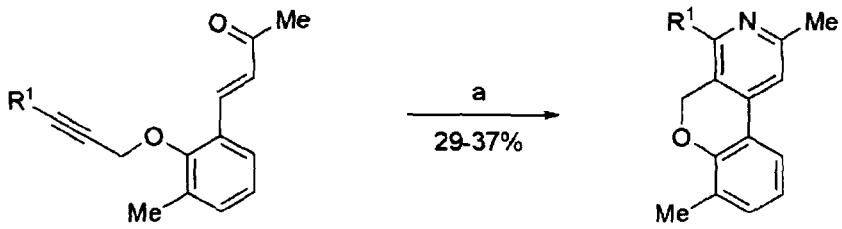
Entry	IMDA Substrate	R^1	Product	Temp/°C	Yield/%
1	**340**	Ph	**344**	180	62
2	**340**	Ph	**344**	140	42
3	**341**	CO_2Me	**345**	180	50
4	**341**	CO_2Me	**345**	140	41
5	**342**	Cl	**346**	180	16[a]
6	**343**	TMS	**335**	200	12[b]

[a] Also isolated was pyridine **335** in 30% yield.

[b] Also isolated was recovered starting material **343** in 69% yield.

However, IMDA reaction of oxime **342** gave only small amounts of the expected 2-chloropyridine **346** (**Table 35**, entry 5), with the main isolated product being pyridine **335** that arises through formal loss of the chlorine atom, although it is not yet clear at which stage this loss occurs. As may be expected, introduction of a bulky TMS group into the dienophile greatly retarded the IMDA reaction (**Table 35**, entry 6), such that even after prolonged heating 69% of the unreacted starting material was recovered, with only 12% of the desilylated pyridine **335** being isolated.

It was also envisioned that direct conversion of the α,β-unsaturated ketones **327** and **339** to the aromatic products would also be possible through a one-pot oxime formation/hetero-Diels-Alder reaction (**Scheme 84**). Pleasingly, treatment of ketones **327** and **339** with methoxylamine hydrochloride and triethylamine in xylene in a sealed tube and heating to 180 °C for 16 h gave the desired pyridines **335** and **344** in 29% and 37% yield respectively (**Table 36**, entries 1 and 2).



327, 339 **335, 344**

Scheme 84. *Reagents and conditions*: a. $MeONH_2 \cdot HCl$, Et_3N, xylene, 180 °C, sealed tube, 16 h.

Table 36. One pot oxime formation/hetero-Diels-Alder reaction of α,β-unsaturated ketones **327-339**.

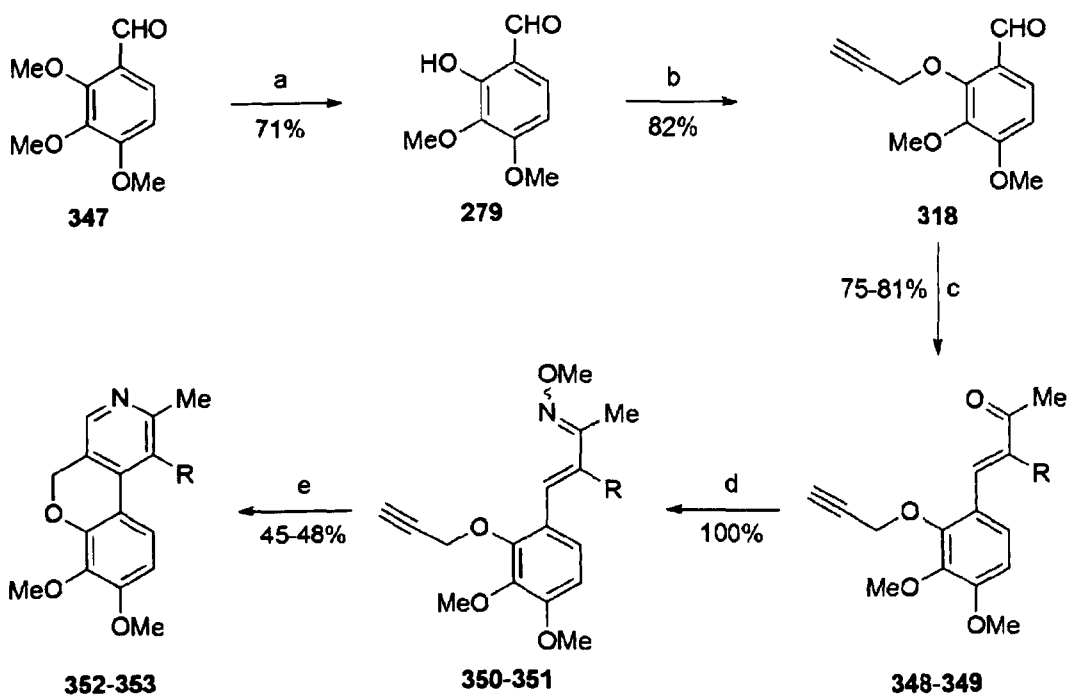
Entry	IMDA Substrate	R^1	Product	Yield/%
1	**327**	H	**335**	29
2	**339**	Ph	**344**	37

Having successfully demonstrated that the intramolecular hetero-Diels-Alder reaction of vinyl oxime ethers with acetylenes represents a rapid and versatile route to a range of [*c*]-annelated pyridines, attention was turned to the preparation of the required hetero-Diels-Alder substrate for the formal synthesis of streptonigrin **215**.

3.6 Synthesis of the Model CD-rings

First, IMDA substrates **350-351** bearing the correct CD-ring substitution pattern for streptonigrin **215** were prepared using the above methodology. The required 3,4-dimethoxysalicaldehyde **279** was readily obtained in multigram quantities from 2,3,4-trimethoxybenzaldehyde **347** by selective demethylation (controlled by the presence of the proximal aldehyde moiety) using aluminium trichloride in benzene (**Scheme 85**).[138] Alkylation of **279** with propargyl chloride[59] and Wadsworth-Emmons

reaction[133] delivered α,β-unsaturated ketones **348-349**. Synthesis of the corresponding hydrazones was attempted on treatment with *N*,*N*-dimethylhydrazine under a range of dehydrating conditions. However formation of Michael adducts precluded isolation of the desired product. In contrast, oxime formation[139] proceeded without incident and in excellent yield to provide IMDA substrates **350-351**. As expected, intramolecular cycloaddition proceeded smoothly to provide the chromeno[*c*]pyridines **352-353** in 45% and 48% yield respectively (**Table 37**, entries 1-2). Direct conversion of ketones **348** and **349** to pyridines **352** and **353** was also achieved in one pot on heating with methoxylamine hydrochloride and triethylamine in xylene in 54% and 56% yield.[132]



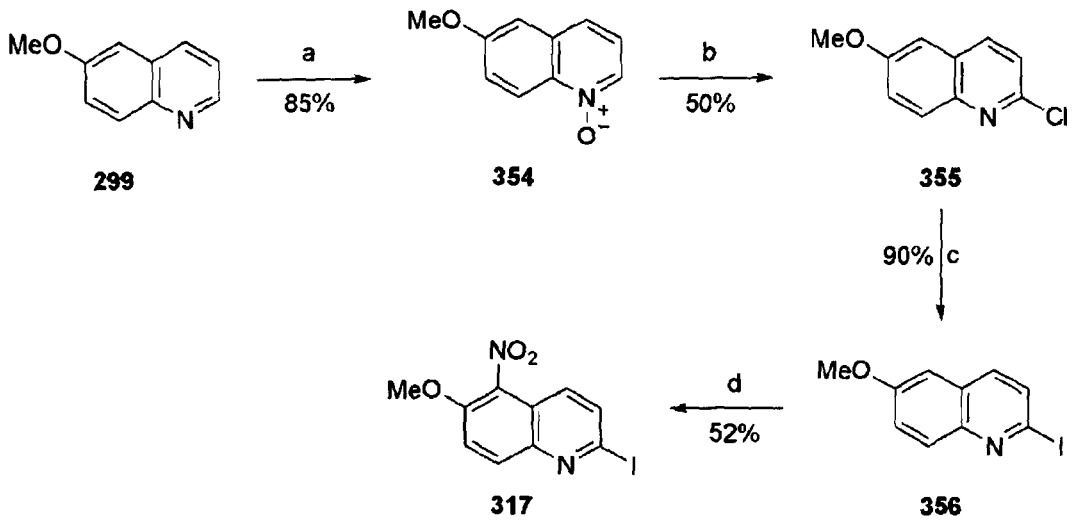
Scheme 85. *Reagents and conditions*: a. $AlCl_3$, benzene, reflux, 6 h; b. $HC{\equiv}CCH_2Cl$, K_2CO_3, EtOH, reflux, 18 h; c. $(EtO)_2P(O)CHRCOMe$, NaH or KO^tBu, DME, rt, 16 h; d. $MeONH_2{\cdot}HCl$, $NaOAc{\cdot}3H_2O$, EtOH, H_2O, 60 °C, 16 h; e. xylene, 180 °C, sealed tube, 16 h.

Table 37. Synthesis of model pyridines **352-353**.

Entry	R	Ketone	Yield/%	Oxime	Yield/%	Pyridine	Yield/%
1	H	**348**	75	**350**	100	**352**	45
2	Me	**349**	81	**351**	100	**353**	48

3.7 Synthesis of the Quinoline AB-Ring Fragment

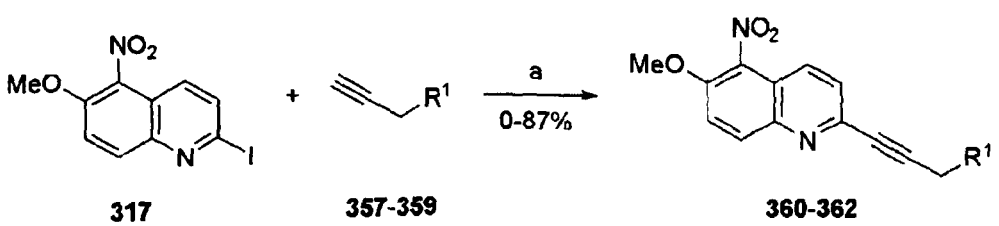
Next, attention was turned to the synthesis of the quinoline AB-ring fragment. In the event, 2-iodo-6-methoxy-5-nitroquinoline **317** was prepared in multigram quantities following literature procedure.[140] Commercially available 6-methoxyquinoline **299** was first converted into its *N*-oxide **354** on heating with hydrogen peroxide in acetic acid (**Scheme 86**). Treatment of **354** with a large excess of phosphorus oxychloride gave a 1:1 mixture of the 2- and 4-chloroquinoline regioisomers, which were separable by flash chromatography, allowing the desired 2-chloro-6-methoxyquinoline **355** to be isolated in 50% yield. Conversion into the iodide **356** was then accomplished on treatment of **355** with sodium iodide in excellent yield. Selective nitration afforded the desired 2-iodo-6-methoxy-5-nitroquinoline **317**.



Scheme 86. *Reagents and conditions*: a. H_2O_2, AcOH, 80 °C, 6 h; b. $POCl_3$, 100 °C, 1 h; c. NaI, 5 M HCl, MeCN, reflux, 16 h; d. HNO_3, H_2SO_4, 0 °C, 45 min.

3.8 Sonogashira Coupling of the AB- and D-ring fragments

The union of quinoline fragment **317** and the D-ring was first envisaged through a Sonogashira cross-coupling strategy.[134] Initial attempts involved the coupling of a 3-carbon propargyl unit with iodoquinoline **317** (**Scheme 87**). A poor yield was obtained using propargyl alcohol **357**, and no reaction was observed with the tosylate[141] **358** under optimised reaction conditions. However, the tetrahydropyranyl (THP) ether of propargyl alcohol **359** gave an excellent yield of the coupled product **362**.[142]

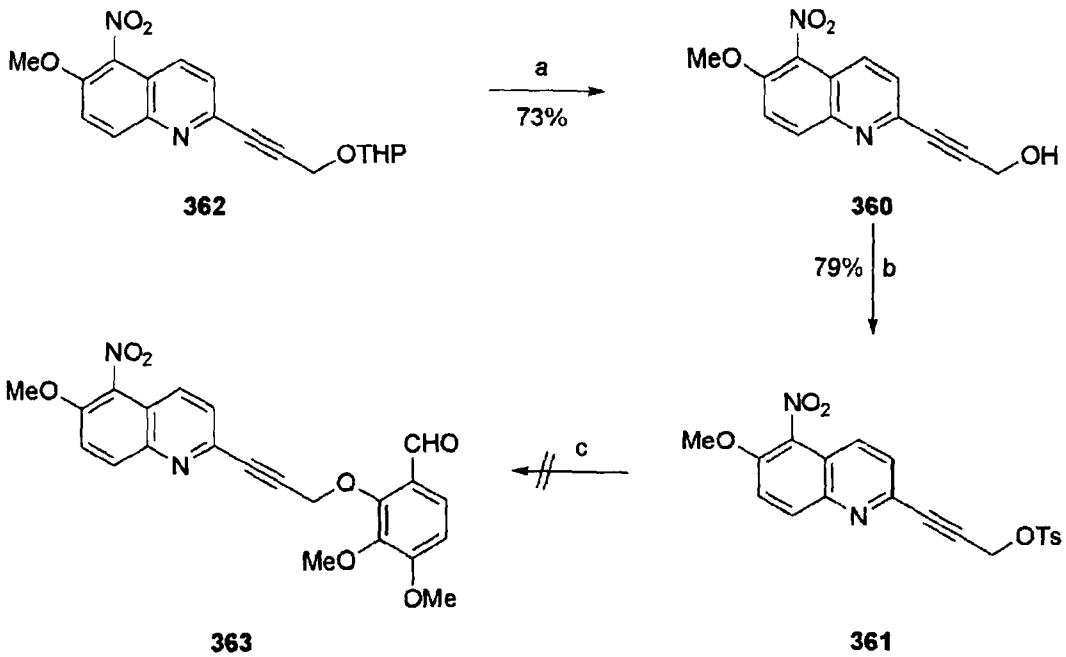


Scheme 87. *Reagents and conditions*: a. $PdCl_2(PPh_3)_2$, CuI, Et_3N, 60 °C, 16 h.

Table 38. Sonogashira coupling of iodoquinoline **317** with acetylenes **357-359**.

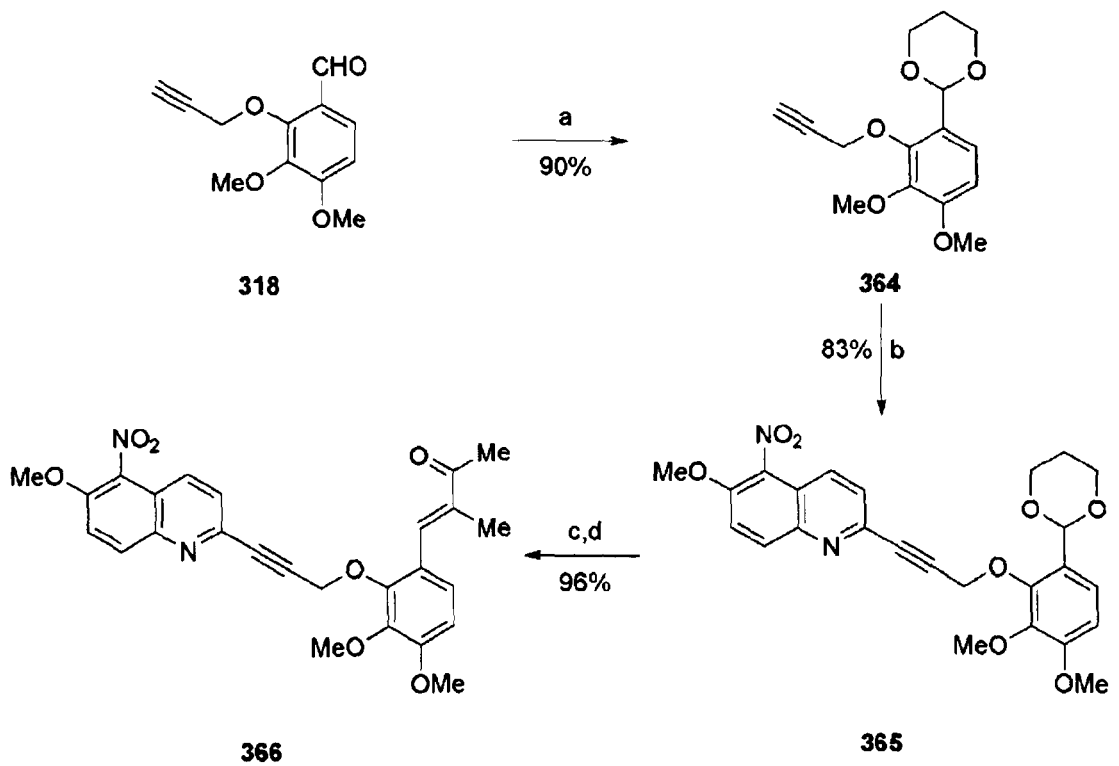
Entry	Acetylene	R^1	Product	Yield/%
1	**357**	OH	**360**	38
2	**358**	OTs	**361**	-
3	**359**	OTHP	**362**	87

Having successfully coupled the propargyl unit onto the AB-ring system of streptonigrin, addition of the D-ring was then envisaged through a simple alkylation strategy. Thus, deprotection of the THP group from **362** was carried out using *para*-toluenesulfonic acid in ethanol in 73% yield (**Scheme 88**). Tosylation of propargylic alcohol **360** was then achieved in good yield under standard conditions.[141] Unfortunately, attempted alkylation of phenol **279** with tosylate **361** using potassium carbonate in ethanol led only to decomposition of the starting materials. Mitsunobu coupling was also attempted between propargyl alcohol **360** and phenol **279**, but only starting material was recovered.[143]



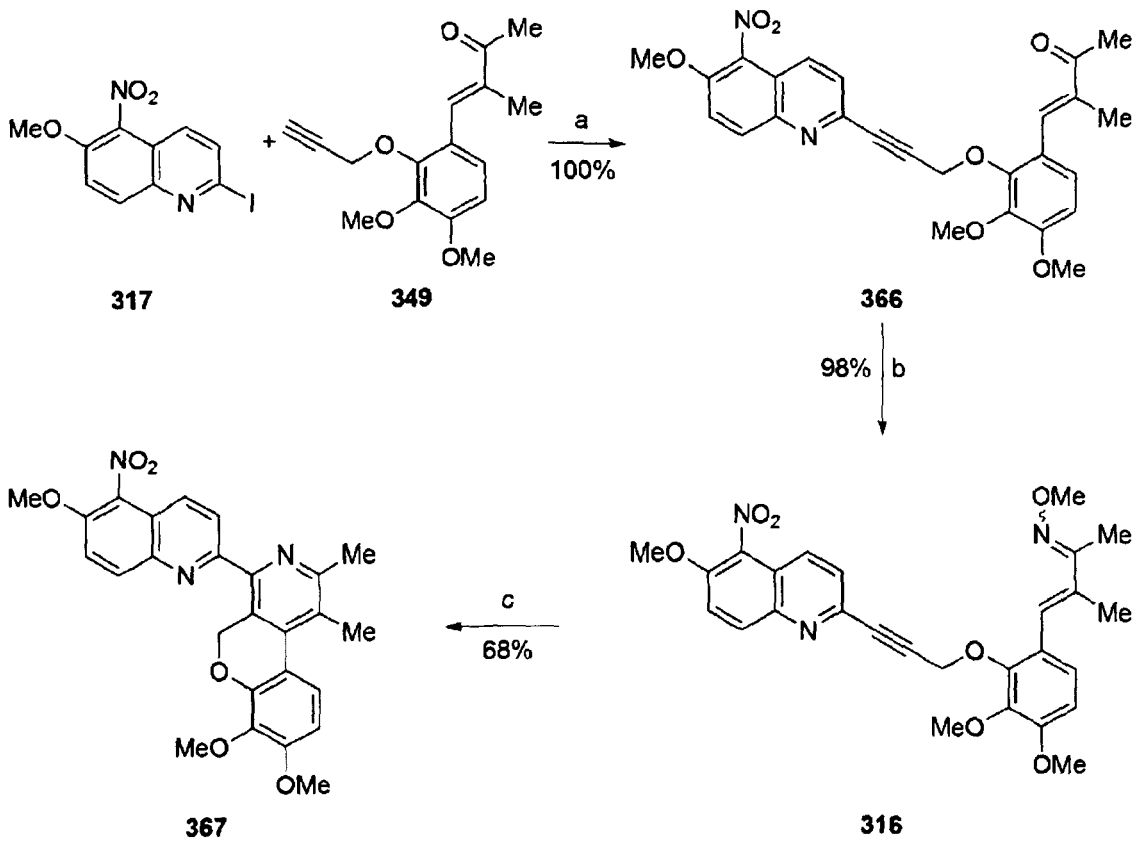
Scheme 88. *Reagents and conditions*: a. *p*-TsOH, EtOH, rt, 2 h; b. NaH, TsCl, THF; c. **279**, K_2CO_3, EtOH, reflux.

Sonogashira reaction using an *O*-propargyl aryl ether as the acetylenic partner was next examined. Initially, the sensitive aldehyde moiety in **318** was protected as its cyclic acetal **364** in excellent yield on treatment with 1,3-propanediol and catalytic *para*-toluenesulfonic acid under Dean-Stark conditions,[144] followed by Sonogashira coupling with iodoquinoline **317** in 83% yield under previously optimised conditions (**Scheme 89**). Deprotection of the acetal was accomplished in quantitative yield on heating **365** in a 9:1 acetic acid/water solvent mixture.[145] The aldehyde was then elaborated into the α,β-unsaturated ketone **366** using a Wadsworth-Emmons reaction as described above.



Scheme 89. *Reagents and conditions*: a. $HO(CH_2)_3OH$, *p*-TsOH, toluene, reflux, Dean-Stark, 18 h; b. **317**, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 60 °C, 16 h; c. AcOH, H_2O, 50 °C, 2 h; d. $(EtO)_2P(O)CHMeCOMe$ **319**, NaH, DME, rt, 16 h.

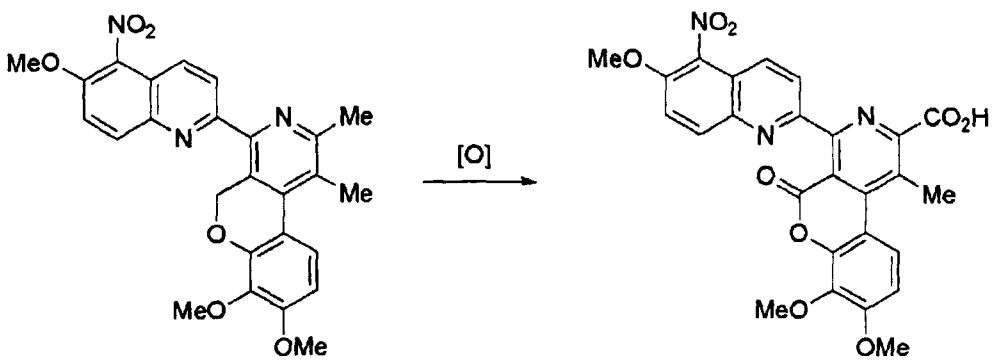
The synthesis was shortened by the discovery that ketone **366** could be prepared by direct cross-coupling of acetylene **349** with iodoquinoline **317**, negating the need for aldehyde protection and deprotection (**Scheme 90**). The 1-aza-1,3-butadiene unit was installed using conditions developed for the model systems, again in excellent yield. IMDA cycloaddition was induced on heating **316** under reflux in xylene for 16 hours, giving the desired penta-substituted pyridine **367** in 68% yield. Thus, synthesis of the complete carbon skeleton of streptonigrin **215** was achieved in just 9 steps (6 steps longest linear sequence).



Scheme 90. *Reagents and conditions*: a. $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, 60 °C, 16 h; b. $MeONH_2 \cdot HCl$, $NaOAc \cdot 3H_2O$, EtOH, H_2O, 60 °C, 16 h; c. xylene, reflux, 16 h.

Oxidation of the benzylic ether and the pyridine methyl group to the corresponding lactone and carboxylic acid were next investigated (**Scheme 91**). Oxidation of simple benzopyrans and 2-methylpyridines have been reported using a variety of oxidants, most commonly chromium based reagents such as pyridinium chlorochromate[146-148] (PCC) and pyridinium dichromate[149] (PDC), or selenium reagents including selenium dioxide[130, 140, 150-152] and selenious acid.[153] Unfortunately, treatment of pyridine **367** with a large range of oxidants, including chromium reagents[146-149, 154-158] (**Table 39**, entries 1-6), selenium reagents[130, 140, 150-153] (**Table 39**, entries 7-9), cerium ammonium nitrate[159] and cerium triflate[160] (**Table 39**, entries 10-11), potassium permanganate[161] (**Table 39**, entry 12) and manganese dioxide[162, 163] (**Table 39**, entry 13). In most cases,

unreacted starting material was recovered, except when using PDC as the oxidant at high temperature under microwave heating, which lead to decomposition (**Table 39**, entry 3). Attempted oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) also led to decomposition of the starting material, presumably through the electron-rich D-ring (**Table 39**, entry 14).[164] Treatment of **367** with isoamyl nitrite and hydrochloric acid under reflux in ethanol led to formation of the pyridine hydrochloride salt (**Table 39**, entry 15), which was converted back into the free base on washing with saturated sodium bicarbonate solution. Oxidation of benzylic ethers has also been reported using ruthenium tetroxide formed *in situ* from ruthenium chloride and sodium periodate.[165, 166] Once again, only starting material was recovered under these conditions (**Table 39**, entry 16). Functionalisation of the activated methylene and methyl groups through radical bromination and lithiation strategies also proved unsuccessful.



367 **368**

Scheme 91. *Reagents and conditions*: see table.

Table 39. Attempted oxidation of pyridine **367**.

Entry	Oxidant	Solvent	Temp./°C	Time/h	Result
1	PCC	CH_2Cl_2	Reflux	16	SM
2	PDC	DMF	30-70 °C	48	SM
3	PDC	DMF	120-180 °C (MW)	6	decomp.
4	Jones	acetone	rt	2	SM
5	CrO_3	Ac_2O H_2SO_4	0 °C	6	SM
6	CrO_2Cl_2	CCl_4	reflux	18	SM
7	SeO_2	xylene	reflux	16	SM
8	SeO_2	AcOH	reflux	16	SM
9	H_2SeO_3	Dioxane H_2O	reflux	20	SM
10	CAN	AcOH H_2O	100 °C	27	SM
11	$Ce(OTf)_4$	MeCN	rt	2	SM
12	$KMnO_4$	acetone	reflux	3	SM
13	MnO_2	dioxane	120-150 °C (MW)	6	SM
14	DDQ	toluene	reflux	20	decomp.
15	Isoamyl nitrite	EtOH, HCl	reflux	3	**367**·HCl salt
16	$RuCl_3.H_2O$ $NaIO_4$	MeCN CCl_4, H_2O	rt	1	SM

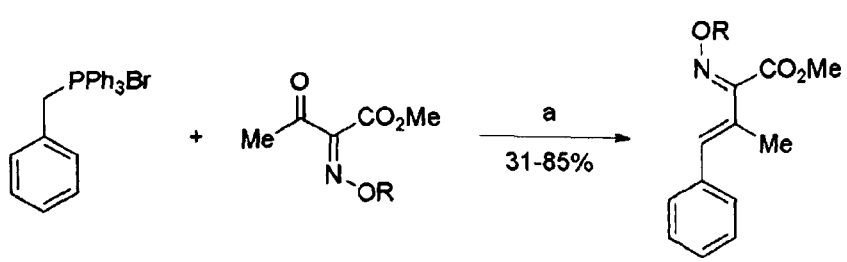
Difficulties in oxidising the pyridine C-2 methyl group have been encountered by both Cheng and DeShong in their syntheses of the CD-rings of streptonigrin **215**. Deshong found that oxidation at this position could not be realised whilst the D-ring was in place due to competing degradation,[131] whilst Cheng and coworkers reported that a

strong electron-withdrawing group *para* to the methyl group was required for oxidation to take place.[130]

3.9 Synthesis of IMDA Substrates Bearing an Ester at C-2 of the 1-Azadiene

Direct incorporation of an ester moiety into the 1-azadiene unit prior to cycloaddition was therefore attempted. Initial attempts centred on a Wittig reaction between an appropriately substituted benzylic phosphonium salt and an α-oximino-β-ketoacetate.

Model Wittig reactions were carried out between the phosphorane derived from benzyltriphenylphosphonium bromide **369** and methyl methoximinoacetoacetate **235** (**Scheme 92**). The best yield previously reported for this reaction was 31% using *n*-butyllithium as base in THF (**Table 40**, entry 1).[167] However, simple modification of the base and solvent allowed the desired alkene **370** to be isolated in 81-85% yield (**Table 40**, entries 2-3). The Wittig reaction between **369** and the TBDMS protected oxime **371** also proceeded smoothly with no loss of the silyl protecting group (**Table 40**, entries 4-5). In both cases potassium *tert*-butoxide was shown to be the superior base, giving the desired alkenes in excellent yield.



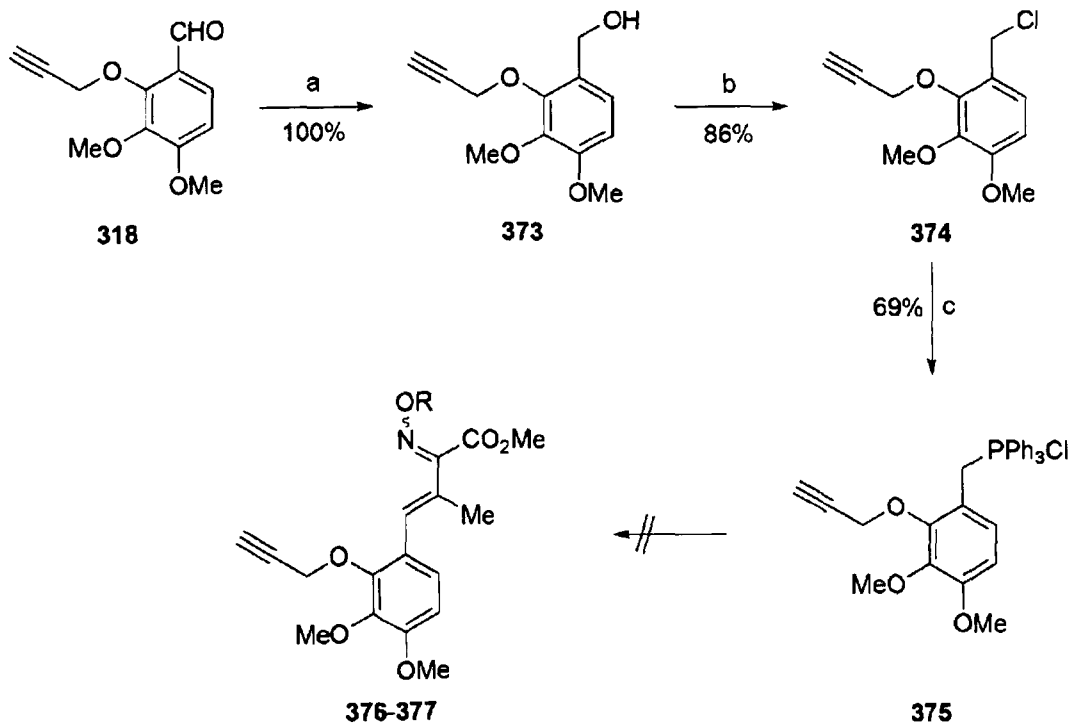
369 **235, 370** **371-372**

Scheme 92. *Reagents and conditions*: a. see table.

Table 40. Model Wittig reactions between benyltriphenylphosphonium bromide **369** and oximinoacetoacetates **235** and **370**.

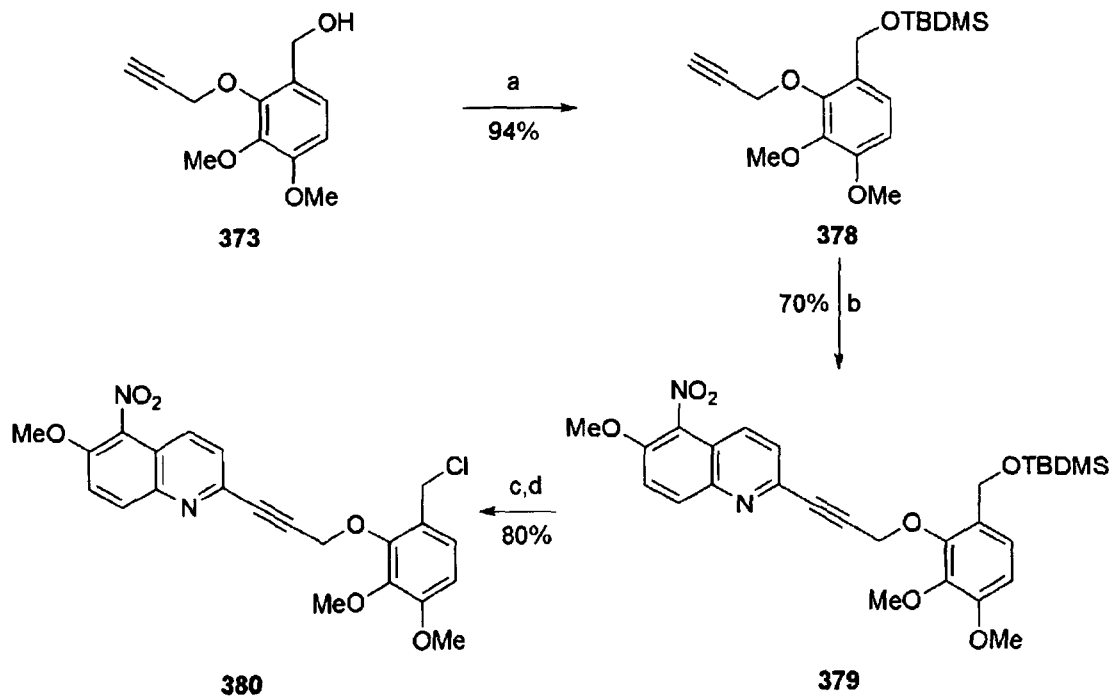
Entry	Oxime	R	Method	Product	Yield/%
1	**235**	OMe	*n*-BuLi, THF -78 °C to rt	**371**	31
2	**235**	OMe	NaH, DME 0 °C to rt	**371**	81
3	**235**	OMe	KO^{t}Bu, DME 0 °C to rt	**371**	85
4	**370**	OTBDMS	NaH, DME 0 °C to rt	**372**	66
5	**370**	OTBDMS	KO^{t}Bu, DME 0 °C to rt	**372**	81

Next, the fully substituted D-ring phosphonium salt **375** was prepared from aldehyde **318** in 3 steps (**Scheme 93**). Reduction of the aldehyde proceeded in quantitative yield on treatment with sodium borohydride in methanol to give the alcohol **373**, which was converted into the chloride **374** in good yield using thionyl chloride and pyridine in ethanol. Formation of the phosphonium salt **375** was achieved on heating **374** with triphenylphosphine in toluene for 18 hours.[168] Wittig reaction between **375** and oximinoacetates **235** and **370** was then attempted using the optimised conditions above. Unfortunately, a mixture of products containing only traces of the desired compound was observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. One possible reason for this could be the presence of the acidic terminal acetylene moiety in **375**.



Scheme 93. *Reagents and conditions*: a. $NaBH_4$, MeOH, 0 °C, 1 h; b. $SOCl_2$, pyridine, CH_2Cl_2, rt, 3 h; c. PPh_3, toluene, 60 °C, 18 h.

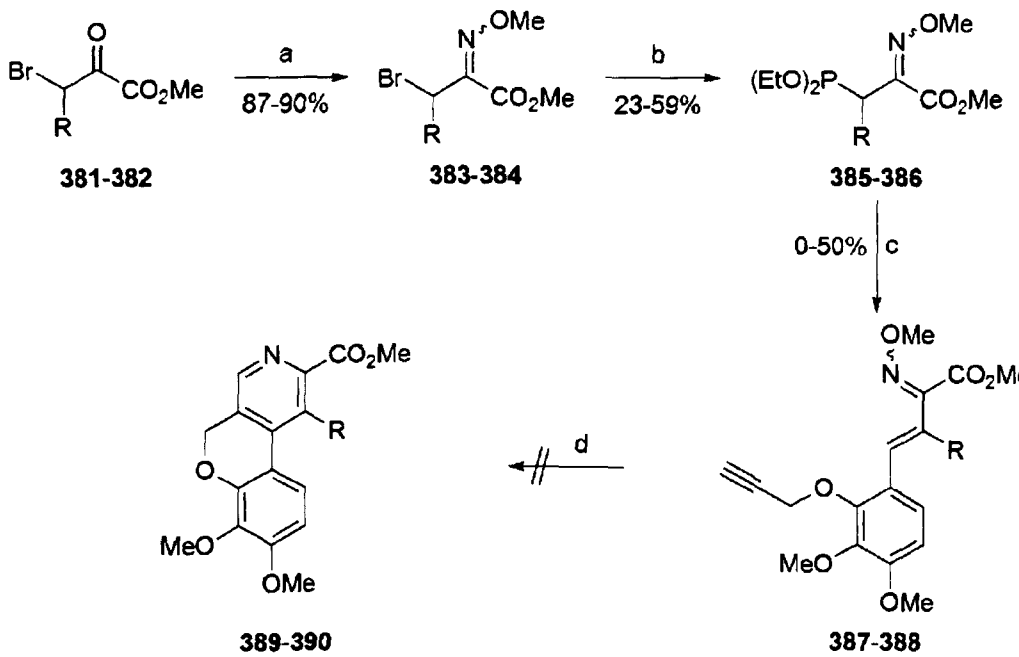
Thus, formation of the phosphonium salt and subsequent Wittig reaction after Sonagashira coupling of the AB- and D-rings was next investigated. Direct reduction of the aldehyde function in **363** led to concomitant reduction of the aromatic nitro group to the corresponding amine. Thus, benzylic alcohol **373** was protected as the TBDMS ether **378** in excellent yield (**Scheme 94**).[169] Once again, cross-coupling of 2-iodo-6-methoxy-5-nitroquinoline **317** with the terminal alkyne was carried out in good yield to afford **379**. Deprotection of the silyl group was achieved on stirring with Dowex-50W™ acidic resin in methanol.[170] Conversion of the resulting alcohol into the chloride **380** was then accomplished using thionyl chloride and pyridine in ethanol.[168] Attempted formation of the Wittig salt on heating **380** with triphenylphosphine led only to decomposition of the starting material, possibly due to the presence of the aromatic nitro group.



Scheme 94. *Reagents and conditions*: a. TBDMSCl, imidazole, CH_2Cl_2, rt, 3 h; b. $PdCl_2(PPh_3)_2$, CuI, Et_3N, 60 °C, 16 h; c. Dowex-50W™, MeOH, rt, 5 h; d. $SOCl_2$, pyridine, CH_2Cl_2, rt, 3 h.

Attention was next turned to installation of the ester group into the 1-azadiene via a Wadsworth-Emmons reaction. The required β-oximinophosphonates **385** and **386** were prepared from methyl bromopyruvate **381** and α-bromo-2-ketobutyric acid methyl ester[171] **382** respectively in two steps on treatment with methoxylamine hydrochloride followed by Arbuzov reaction with trimethyl phosphite (**Scheme 95**).[172] Wadsworth-Emmons reaction using potassium *tert*-butoxide as base failed to afford any of the desired products, most likely due to the decreased acidity of the α-proton in **385-386** compared to the β-ketophosphonates used previously. Switching to *n*-butyllithium as a stronger base allowed formation of α,β-unsaturated oxime **387**, although no reaction was still observed with more hindered phosphonate **386**. The deactivating effect of the ester moiety on 1-azadiene **387** proved to be too great, as

intramolecular cycloaddition was not observed at temperatures up to 180 °C. This route was therefore abandoned.



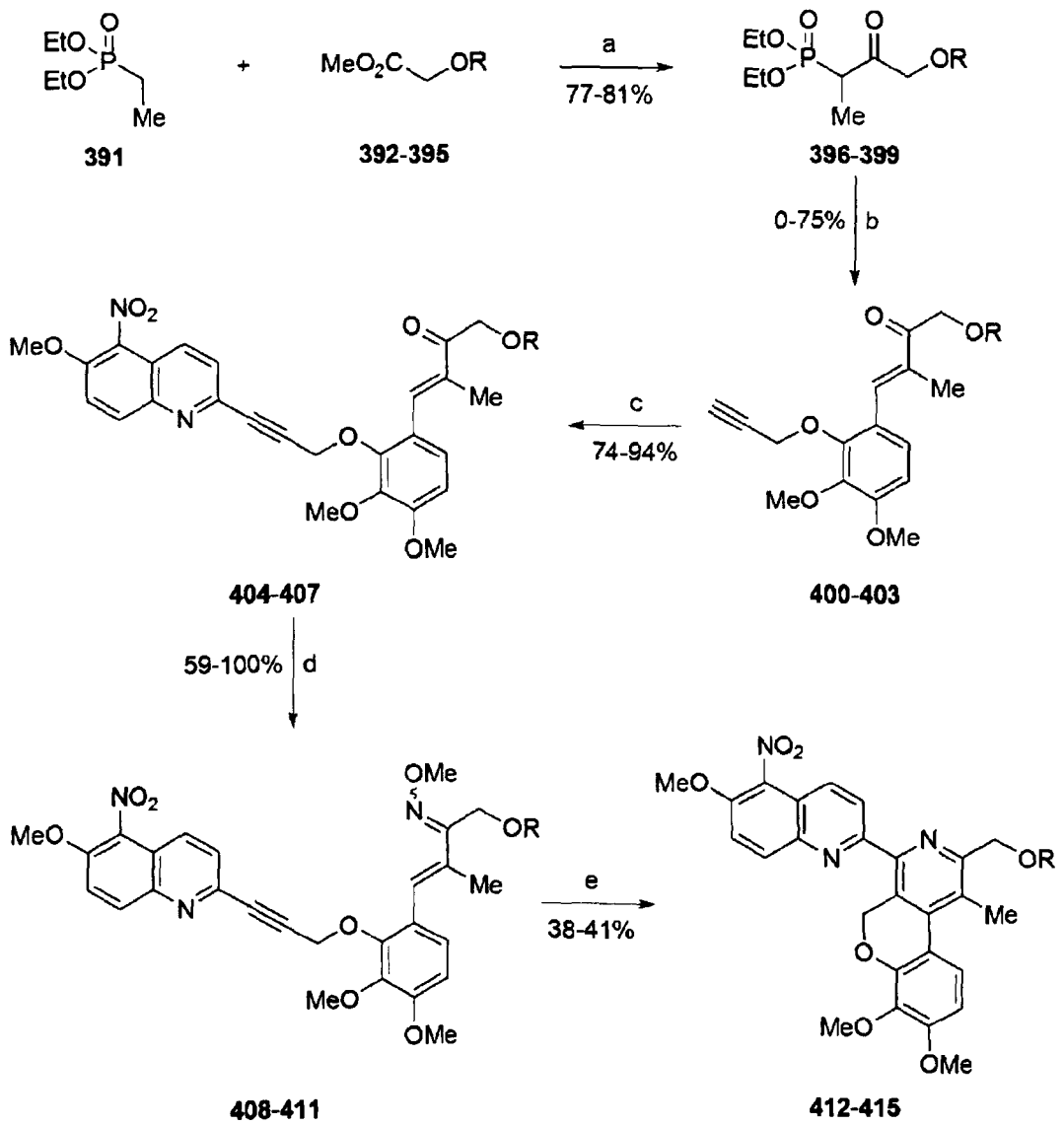
Scheme 95. *Reagents and conditions*: a. MeO-NH_2·HCl, MeOH, 16 h; b. $P(OEt)_3$, reflux, 48 h; c. **318**, *n*-BuLi, THF, -78 °C to rt, 16 h; d. xylene, 180 °C, sealed tube, 16 h.

Table 41. Synthesis of IMDA substrates bearing an ester at C-2.

Entry	R	Oxime	Yield/%	Phosphonate	Yield/%	IMDA Substrate	Yield/%
1	H	**383**	90	**385**	59	**387**	50
2	Me	**384**	87	**386**	23	**388**	-

3.10 Introduction of Oxygen Functionality into the Diene

In order to promote the oxidation of the pyridine C-2 methyl group without compromising 1-azadiene reactivity, oxygen functionality was introduced at an earlier stage in the synthesis (**Scheme 96, Table 42**). Thus, β-ketophosphonates **396-399** were prepared by acylation of the carbanion of diethyl ethylphosphonate[133] **391** with protected methyl glycolates **392-395**, themselves obtained from methoxyacetic acid or glycolic acid.[173-177] First, TBDMS protected phosphonate **396** was examined in the Wadsworth-Emmons reaction with **318**. Unfortunately, loss of the protecting group was observed under the reaction conditions. Phosphonates **397-399** bearing the more hydrolytically stable allyl, methyl and PMB protecting groups however delivered the desired α,β-unsaturated ketones **401-403** in good yield. Elaboration of the terminal acetylenes via a Sonogashira reaction proceeded without incident to give **405-407**, followed by formation of the corresponding oximes **409-411**. Attempted IMDA cycloaddition of allyl protected substrate **405** led to formation of a complex mixture of products on heating in xylene at 180 °C for 16 hours. However, the required penta-substituted pyridines **414** and **415** were obtained from **410** and **411**, albeit in modest yield, under the same conditions.

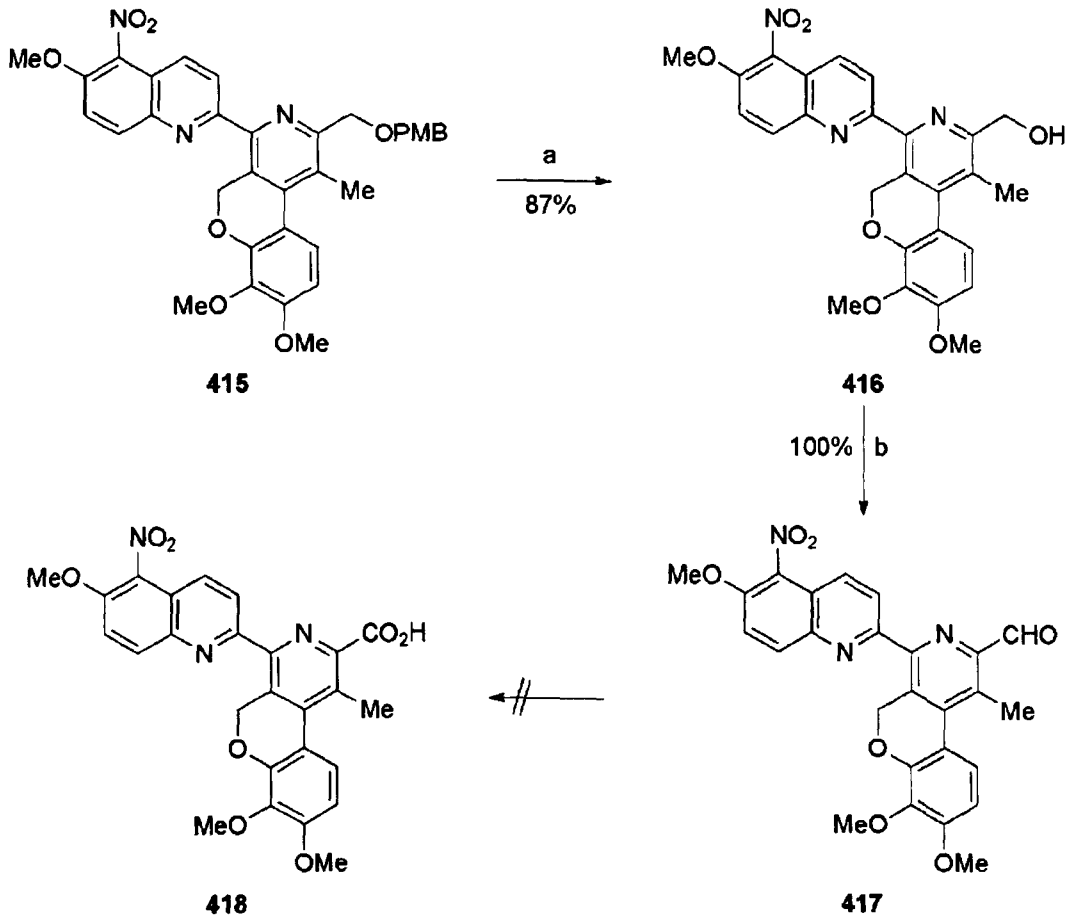


Scheme 96. *Reagents and conditions*: a. **391**, *n*-BuLi, THF, -78 °C, 1 h then **392-395**, THF, -78 °C to rt, 16 h; b. **318**, KO^{t}Bu, toluene, rt, 16 h; c. **317**, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 60 °C, 16 h; d. $MeONH_2 \cdot HCl$, $NaOAc \cdot 3H_2O$, EtOH, H_2O, 60 °C, 16 h; e. xylene, 180 °C, sealed tube, 16 h.

Table 42. Synthesis of functionalised pyridines **412-415**.

Entry	R	Ketone	Yield/%	Ketone	Yield/%	Pyridine	Yield/%
1	OTBDMS	**400**	-	**404**	-	**412**	-
2	OAllyl	**401**	38	**405**	82	**413**	-
3	OMe	**402**	64	**406**	74	**414**	41
4	OPMB	**403**	75	**407**	94	**415**	38

Removal of the protecting groups was then investigated. Demethylation from methoxymethylpyridine **414** was attempted under a range of conditions, including boron trichloride,[131] boron tribromide and *in situ* generated trimethyliodosilane. Unfortunately, unreacted starting material was recovered in each case. However, removal of the PMB group from **415** was readily effected on treatment with trifluoroacetic acid in the presence of anisole in excellent yield (**Scheme 97**).[178] Although oxidation of the hydroxymethyl group to the aldehyde **417** was accomplished using various reagents including activated manganese dioxide in chloroform,[179] as evidenced by NMR spectroscopic analysis of the crude reaction mixture, further oxidation to the desired carboxylic acid **418** could not be achieved under a range of conditions, such as sodium chlorite[180] and silver nitrate. Direct conversion of **416** to the carboxylic acid was also unsuccessful.



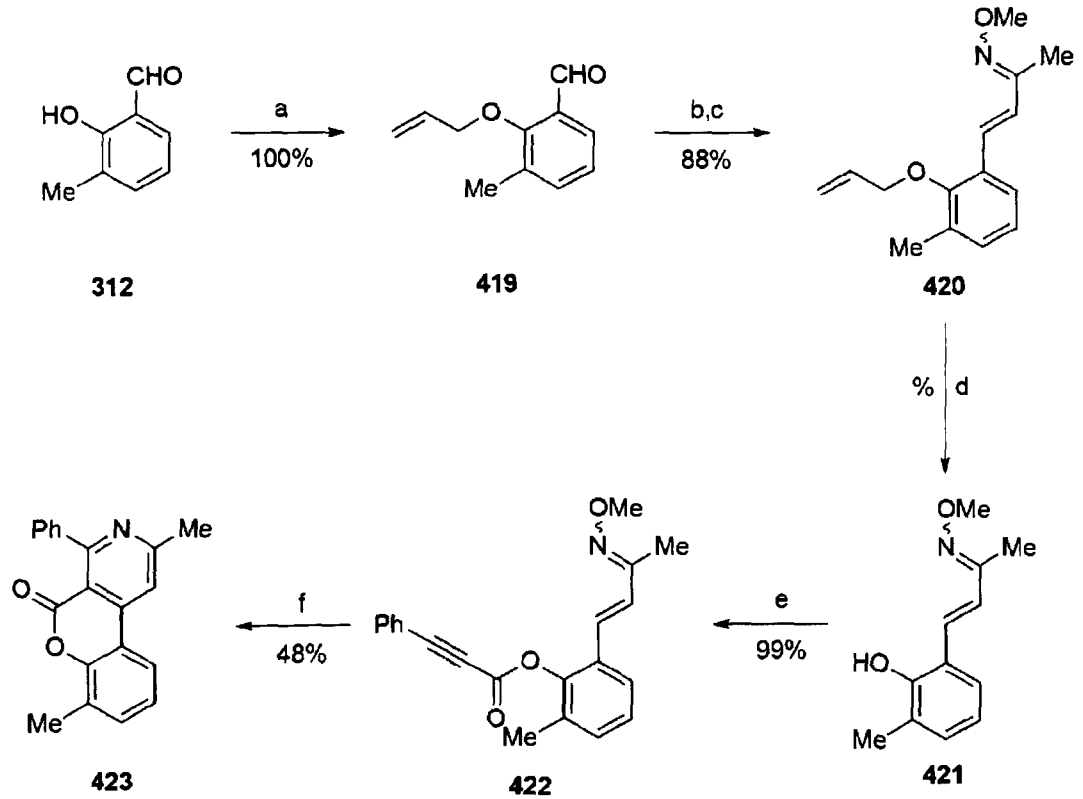
Scheme 97. *Reagents and conditions*: a. TFA, anisole, CH_2Cl_2, rt, 2 h; b. MnO_2, $CHCl_3$, rt, 2 h.

3.11 Synthesis and IMDA Reactions of Model Propiolate Esters

Cheng and coworkers have previously observed that oxidation of a pyridine C-2 methyl group could not be achieved in their synthesis of the CD-rings of streptonigrin **215** unless a strong electron-withdrawing group was present in the *para*-position.[130] Synthesis and intramolecular hetero-Diels-Alder reaction of substrates containing a propiolate ester linker was therefore examined. The ester moiety would have the twin function of introducing the required lactone carbonyl group prior to cycloaddition,

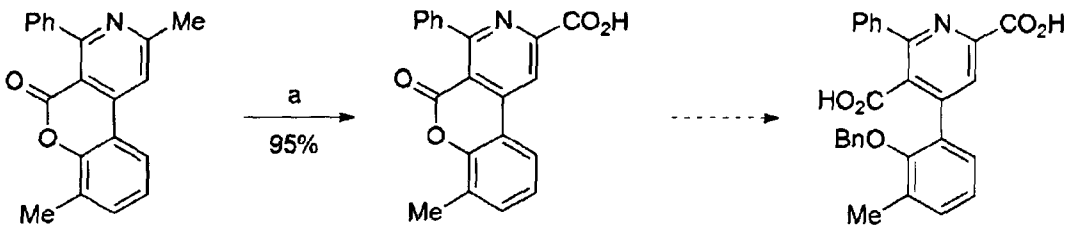
obviating the need for later oxidation, as well as promoting oxidation of the *para* methyl group.

In order to determine whether this was a viable strategy, a suitable model system was constructed. The hydroxyl function in 3-methylsalicaldehyde **321** was first protected as its allyl ether **419**, followed by Wadsworth-Emmons reaction and oxime formation to introduce the 1-azadiene unit **420** (**Scheme 98**). The allyl group was removed on treatment with catalytic palladium(II) acetate, triphenylphosphine and morpholine to reveal phenol **421**. The propiolate ester **422** was then obtained in almost quantitative yield via coupling of **421** with phenylpropiolic acid chloride, formed *in situ* from the free acid using thionyl chloride in dichloromethane.[181] Pleasingly, intramolecular cycloaddition proceeded without incident on heating at 180 °C in xylene for 24 hours in a sealed tube to provide the penta-substituted pyridine **423** in 48% yield.



Scheme 98. *Reagents and conditions*: a. $H_2C{=}CCCH_2Br$, K_2CO_3, EtOH, reflux, 16 h; b. $(MeO)_2P(O)CH_2COMe$, KO^{t}Bu, DME, rt, 16 h; c. $MeONH_2{\cdot}HCl$, $NaOAc{\cdot}3H_2O$, EtOH, H_2O, 60 °C, 16 h; d. $Pd(OAc)_2$, PPh_3, morpholine, THF, rt, 16 h; e. $PhC{\equiv}CCO_2H$, $SOCl_2$, CH_2Cl_2, 40 °C, 16 h then **421**, K_2CO_3, DMF, rt, 16 h; f. xylene, 180 °C, sealed tube, 24 h.

Next, the key methyl group oxidation was attempted. In the event, oxidation of **423** to carboxylic acid **424** was achieved in a single step and in quantitative yield on treatment with selenium dioxide under reflux in pyridine (**Scheme 99**).[140] Subsequent steps to prove that the lactone could be opened to a diacid related to that necessary for the formal synthesis of streptonigrin **215** were then examined. Lactone **424** proved resistant to hydrolysis under mild conditions such as lithium hydroxide in aqueous THF at room temperature. More forcing conditions therefore need to be examined to effect the required transformation, although this has yet to be achieved.[182]

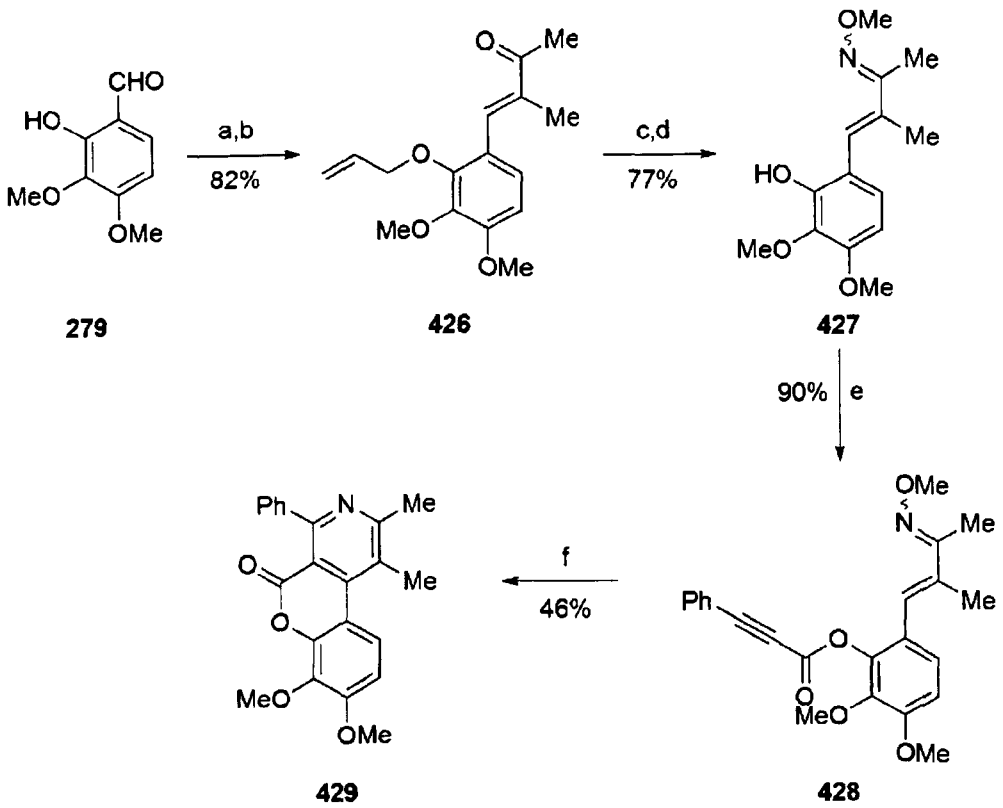


423 424 425

Scheme 99. *Reagents and conditions*: a. SeO_2, pyridine, reflux, 16 h.

Having proved that oxidation of the pyridine C-2 methyl group was possible when activated by a suitable electron-withdrawing group, the same sequence of reactions was used to prepare a substrate bearing the correct D-ring substitution and the extra methyl group present on the pyridine ring. This was to ascertain whether competing oxidation of the pyridine C-3 methyl group or oxidative degradation of the electron-ring D-ring would interfere with the desired transformation.

Thus, starting from 3,4-dimethoxysalicaldehyde **279**, protection of the phenol, Wadsworth-Emmons reaction, formation of the oxime and removal of the allyl group delivered phenol **427** in 63% yield over 4 steps (**Scheme 100**). Formation of phenylpropiolate ester **428** was carried out using identical conditions to those used above. Intramolecular hetero-Diels-Alder reaction generated the pyridine **429** in 46% yield. Unfortunately, attempted methyl group oxidation using selenium dioxide in pyridine led to decomposition of the starting material, presumably due to the electron-rich D-ring. One possible solution to this problem would be formation of the corresponding *N*-oxide and treatment with acetic anhydride to provide the 2-acetoxymethylpyridine which could be further oxidised to the carboxylic acid, although this has yet to be achieved.



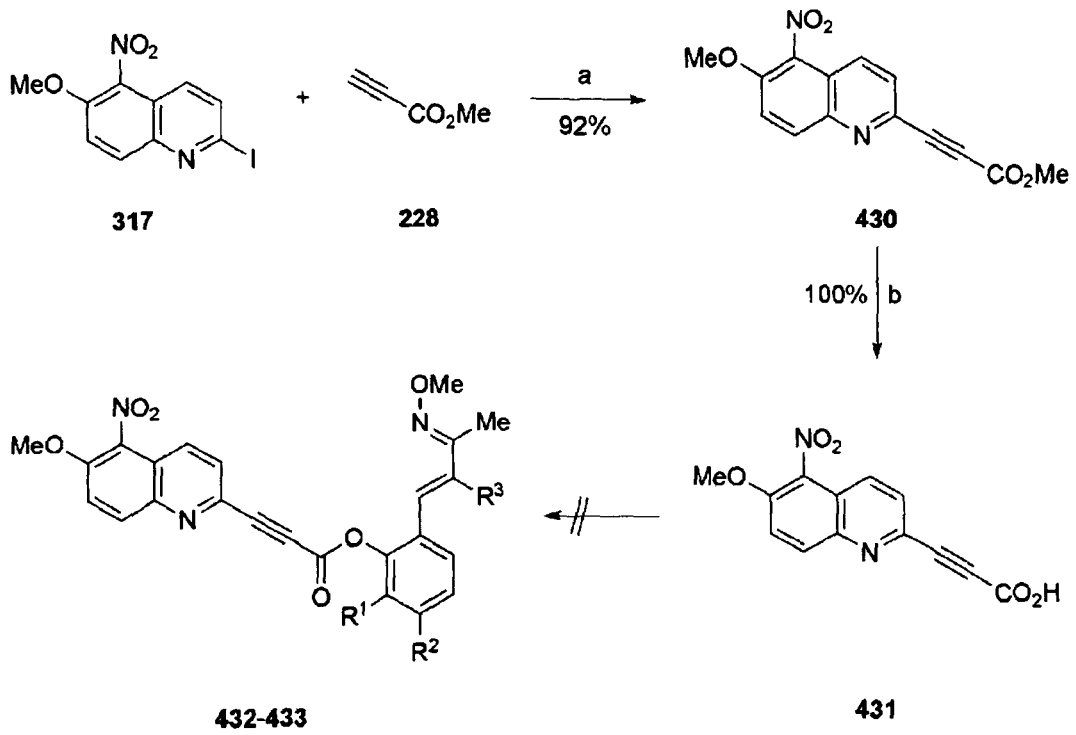
Scheme 100. *Reagents and conditions*: a. $H_2C{=}CCH_2Br$, K_2CO_3, EtOH, reflux, 16 h; b. $(MeO)_2P(O)CHMeCOMe$, KO^{t}Bu, DME, rt, 16 h; c. $MeONH_2{\cdot}HCl$, $NaOAc{\cdot}3H_2O$, EtOH, H_2O, 60 °C, 16 h; d. $Pd(OAc)_2$, PPh_3, morpholine, THF, rt, 16 h; e. $PhC{\equiv}CCO_2H$, $SOCl_2$, CH_2Cl_2, 40 °C, 16 h then **427**, K_2CO_3, DMF, rt, 16 h; f. xylene, 180 °C, sealed tube, 24 h.

3.12 Propiolate Ester Synthesis

In order to prepare a propiolate ester bearing the quinoline AB-ring necessary for streptonigrin **215**, the appropriately substituted propiolic acid **431** was required. Only a handful of examples of Sonogashira reactions using propiolate esters as the acetylenic partner have been reported.[183-191] However, cross-coupling of iodoquinoline **317** with methyl propiolate **228** proceeded without incident to provide **430** in 59% yield (**Scheme 101**). Reoptimisation of the reaction conditions led to an improved yield of 92% using DIPEA as the base. Hydrolysis of the ester was achieved in

quantitative yield under basic conditions using lithium hydroxide in aqueous THF.[189, 192]

Attention was next turned to formation of the required propiolate ester **432**. Initial attempts involved formation of the acid chloride in analogous fashion to the model systems prepared above. Unfortunately, treatment of **431** with an excess of thionyl chloride in dichloromethane followed by phenol **421** and potassium carbonate in DMF led to recovery of the starting phenol (**Table 43**, entry 1).[181] More forcing conditions, including heating **431** in neat oxalyl chloride or thionyl chloride followed by addition of phenol **421** and base once again led to recovery of the starting material (**Table 43**, entries 2-3). Formation of the acid chloride via the carboxylate salt initially proved unsuccessful, most likely due to insolubility of the free acid in the reaction solvents (**Table 43**, entries 4-5).[193] The carboxylate salt was eventually obtained directly from the more soluble methyl ester on treatment with potassium trimethylsilanolate in THF. Analysis of the product by infrared (IR) spectroscopy showed a large shift for the carbonyl peak from 1730 cm^{-1} to 1600 cm^{-1}, which is indicative for the formation of the carboxylate salt. Conversion to the acid chloride was achieved on stirring with oxalyl chloride in dichloromethane, again evidenced by shift of the carbonyl peak in the IR spectrum (1600 cm^{-1} to 1750 cm^{-1}). Unfortunately, only a trace of the desired product was observed after reaction with phenol **427** under basic conditions (**Table 43**, entry 6). Esterification via the mixed anhydride (**Table 43**, entry 7) and acyl imidazolium salt (**Table 43**, entry 8), or under Corey-Nicolaou[194] and Mukaiyama macrolactonisation conditions (**Table 43**, entries 9-10) all failed to give any of the desired product.



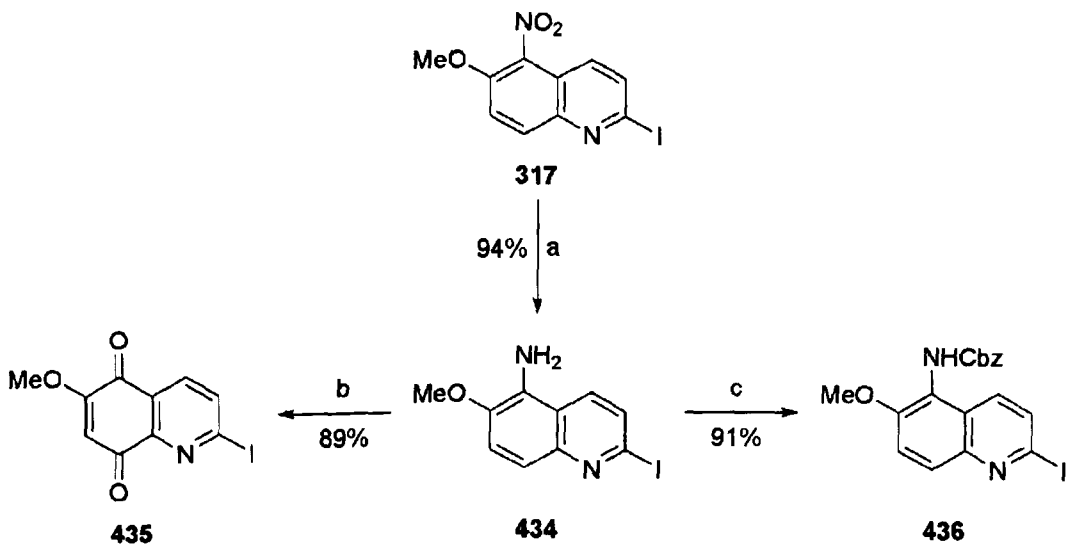
Scheme 101. *Reagents and conditions*: a. $PdCl_2(PPh_3)_2$, CuI, DIPEA, THF, 50 °C, 3 h; b. $LiOH{\cdot}H_2O$, THF, H_2O, rt, 3 h.

Table 43. Attempted formation of propiolate esters **432-433**.

Entry	R^1	R^2	R^3	Conditions	Product	Result
1	Me	H	H	1. $SOCl_2$, CH_2Cl_2, 40 °C	**432**	recovered
				2. **421**, K_2CO_3, DMF		**421**
2	Me	H	H	1. $(COCl)_2$, reflux, x h	**432**	recovered
				2. **421**, K_2CO_3, DMF		**421**
3	Me	H	H	1. $SOCl_2$, reflux, x h	**432**	recovered
				2. **421**, K_2CO_3, DMF		**421**
4	Me	H	H	1. NaOMe, MeOH	**432**	recovered
				2. $(COCl)_2$, PhH		**421**
				3. **421**, K_2CO_3, DMF		
5	Me	H	H	1. NaH, THF	**432**	recovered
				2. $(COCl)_2$, PhH		**421**
				3. **421**, K_2CO_3, DMF		
6	Me	H	H	1. KOTMS, THF	**432**	trace **432**
				2. $(COCl)_2$, CH_2Cl_2		
				3. **421**, K_2CO_3, DMF		
7	OMe	OMe	Me	1. 2,4,6-trichlorobenzoyl	**433**	recovered
				chloride, Et_3N, THF, 110 °C		**427**
				2. **427**, DMAP, THF		
8	OMe	OMe	Me	1. CDI, CH_2Cl_2, reflux	**433**	recovered
				2. **427**, DMAP (cat.)		**427**
9	OMe	OMe	Me	**427**, Py_2S_2, PPh_3	**433**	recovered
				xylene, reflux		**427**
10	OMe	OMe	Me	**427**, 1-methyl-2-	**433**	recovered
				chloropyridinium iodide, Et_3N,		**427**
				CH_2Cl_2, reflux		

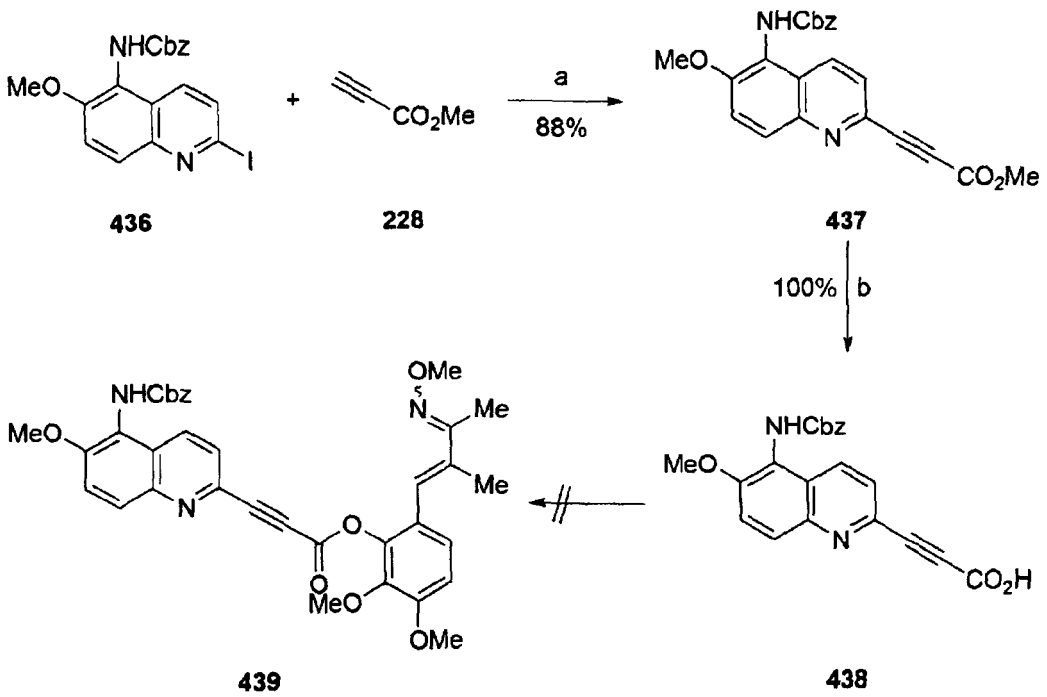
In an attempt to verify **431** as the correct structure, several attempts to grow crystals were made using both vapour- and solvent-diffusion techniques and in a wide variety of solvents. Unfortunately, crystallisation provided only thin needles that were unsuitable for X-ray analysis. In order to determine whether the failure of **431** to undergo esterification was due to some property inherent in that particular system, two

derivatives were synthesised. Thus, reduction of the nitro group in **317** was achieved in 94% yield on heating in ethanol in the presence of iron powder and acetic acid (**Scheme 102**).[195] Oxidation with Fremy's salt delivered quinone **435**. Aniline **434** was also protected as its benzyl carbamate **436**.



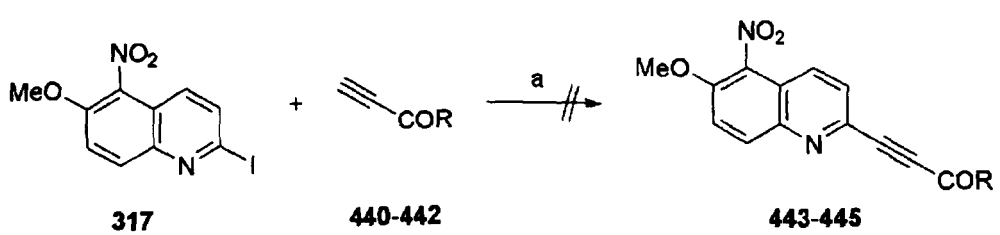
Scheme 102. *Reagents and conditions*: a. Fe (powder), AcOH, EtOH, reflux, 4 h; b. Fremy's salt, NaH_2PO_4 (0.3 M in H_2O), acetone, rt, 12 h; c. benzyl chloroformate, DIPEA, THF, rt, 16 h.

Sonogashira cross-coupling of **435** or **436** with methyl propiolate **228** was then examined. Although quinone **435** failed to give any of the desired coupled product under the standard conditions, **437** was obtained from iodoquinoline **436** in good yield (**Scheme 103**). Hydrolysis of the ester was carried out as before to afford propiolic acid **438**. As was observed for nitroquinoline **431**, several attempts to form the desired ester **439** using a variety of conditions, including via the acid chloride, mixed anhydride and DCC activated ester, resulted in recovery of the starting phenol **427**.



Scheme 103. *Reagents and conditions*: a. $PdCl_2(PPh_3)_2$, CuI, DIPEA, 50 °C, 3 h; b. $LiOH{\cdot}H_2O$, THF, H_2O, rt, 1 h.

Direct Sonogashira coupling of activated propiolate esters[196] **440-442** with iodoquinoline **317** was also attempted. However recovery of the iodide and degradation of the acetylene was observed in each case (**Scheme 104**).

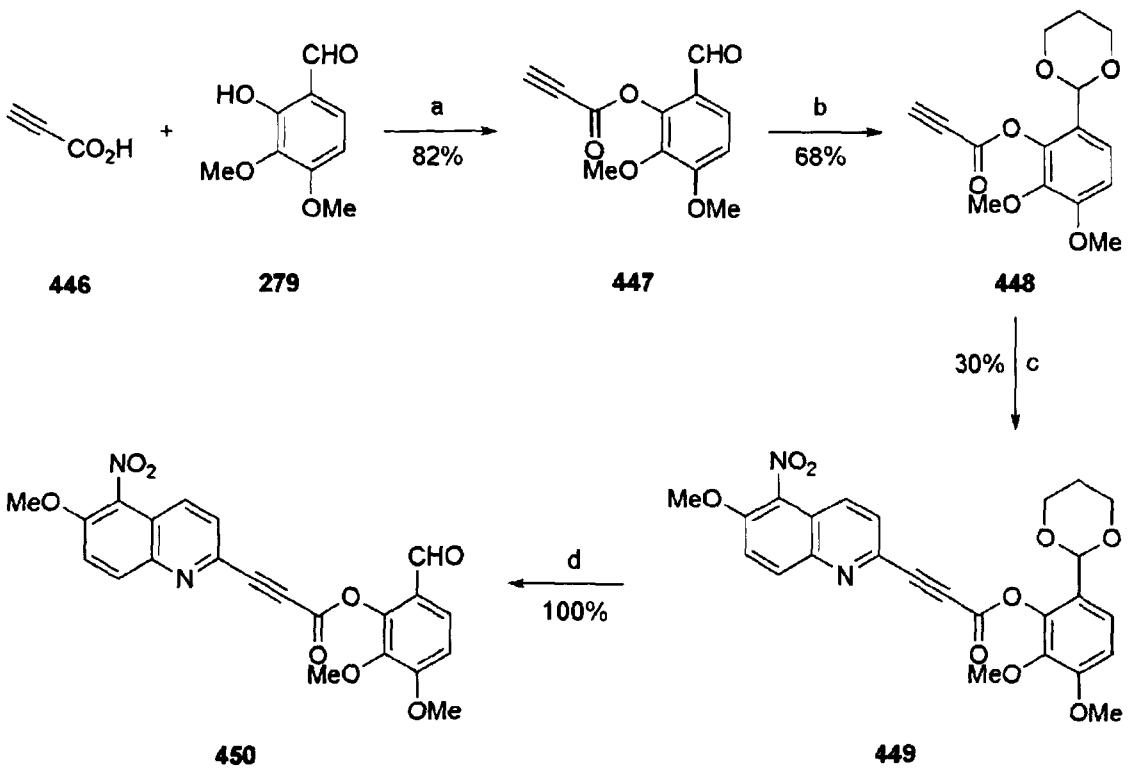


Scheme 104. *Reagents and conditions*: a. $PdCl_2(PPh_3)_2$, CuI, Et_3N, 60 °C, 16 h.

Table 44. Sonogashira reactions between iodoquinoline **317** and activated esters **440-442**.

Entry	Activated Ester	R	Product	Result
1	**440**	Bt	**443**	recovered **317**
2	**441**	OPFP	**444**	recovered **317**
3	**442**	$OC_6H_5(p\text{-}NO_2)$	**445**	recovered **317**

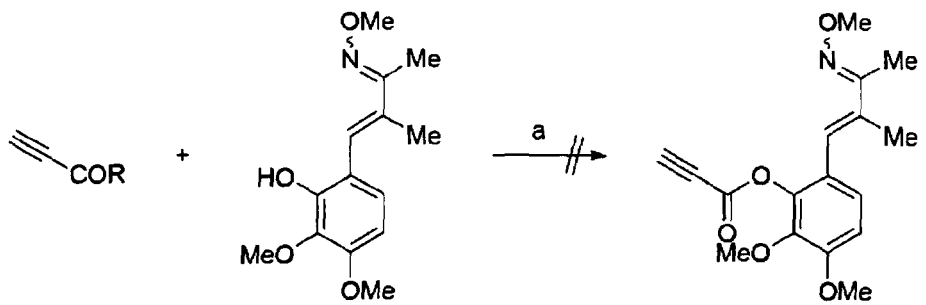
Sonogashira coupling of D-ring phenyl propiolate ester **448** was next investigated. First, formation of the activated ester of propiolic acid **446** was achieved using dicyclohexylcarbodiimide (DCC) and catalytic 4-dimethylaminopyridine (DMAP), followed by coupling with salicaldehyde **279** in good yield to give **447** (**Scheme 105**). Protection of the aldehyde as the 6-membered cyclic acetal under Dean-Stark conditions provided acetylene **448**, which underwent smooth palladium-catalysed cross-coupling with iodoquinoline **317** to afford **449**. Acidic hydrolysis delivered aldehyde **450** ready for elaboration into the α,β-unsaturated ketone via a Wadsworth-Emmons reaction. Unfortunately, cleavage of the labile phenolate ester moiety was observed on treatment with the carbanion derived from β-ketophosphonate **319**, leading to recovery of salicaldehyde **279**.



Scheme 105. *Reagents and conditions*: a. DCC (1 M in CH_2Cl_2), DMAP, CH_2Cl_2, rt, 1 h; b. $HO(CH_2)_3OH$, *p*-TsOH, toluene, reflux, Dean-Stark, 18 h; c. **317**, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 60 °C, 16 h; d. AcOH, H_2O, 50 °C, 2 h.

Due to the difficulties previously encountered in trying to prepare IMDA substrates **432-433**, an esterification/Sonogashira strategy was next envisaged. First, coupling of propiolic acid **446** with phenol **427** was attempted via the activated ester (**Scheme 106**). Treatment of **446** and **427** with DCC in the presence of catalytic DMAP led to a complex mixture of products, due to the formation of Michael adducts competing with the desired transformation (**Table 45**, entry 1). Similar results were obtained using acyl benzotriazole[196] **440**, pentafluorophenyl (PFP) ester **441** and *para*-nitrophenyl ester **442** (**Table 45**, entries 2-4). Propiolic acid chloride **451** has previously been synthesised by treating propiolic acid **446** with phosphorus pentachloride, though isolation must be carried out at low temperature (-135 °C) and under an inert atmosphere as **451** has been reported to spontaneously ignite in air, possibly due to

traces of monochloroacetylenes formed under the reaction conditions.[197] Schirok and coworkers however have reported the *in situ* generation of propiolic acid chloride **451** under mild conditions using Ghosez's reagent.[198] Esterification using this method was attempted, but once again a complex mixture of inseparable products was obtained (**Table 45**, entry 5).



440-442
446,451

427

452

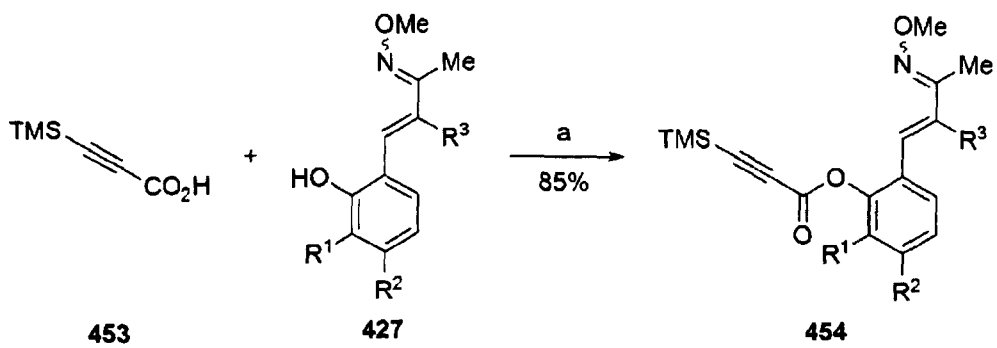
Scheme 106. *Reagents and conditions*: a. See table.

Table 45. Attempted coupling of phenol **427** with activated esters **440-442**, **446** and **451**.

Entry	Activated Ester	R	Conditions	Result
1	**446**	OH	DCC, DMAP (cat.) CH_2Cl_2	complex mixture
2	**440**	Bt	DMAP, THF 65 °C (MW)	complex mixture
3	**441**	OPFP	DMAP, THF	complex mixture
4	**442**	$OC_6H_5(p\text{-}NO_2)$	DMAP, THF	complex mixture
5	**451**	Cl	Ghosez's reagent CH_2Cl_2	complex mixture

A blocking substituent in the form of a TMS group at the alkyne terminus allowed formation of the required esters **454-455** in 85-92% yield via the known

trimethylsilylpropiolic acid chloride (**Scheme 107, Table 46**).[199] Attempted removal of the silicon group from **454** under basic conditions using potassium carbonate in methanol led to cleavage of the labile ester group and recovery of phenol **421**. Degradation of the starting material was also observed on treatment with tetrabutylammonium fluoride (TBAF). Unreacted started material however was recovered using hydrogen fluoride triethylamine complex as the fluoride source. Desilylation was also attempted under acidic conditions, but starting material was once again recovered in each case.



453 **427** **454**

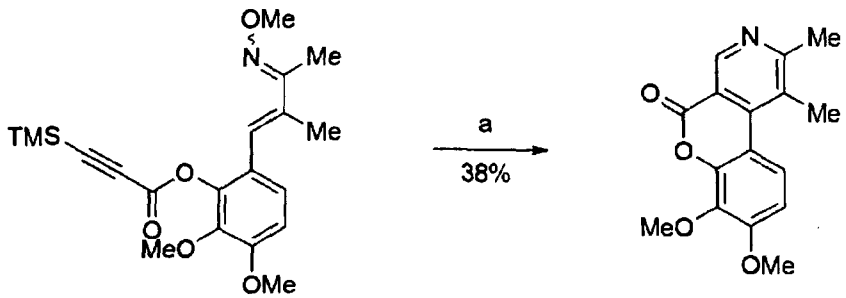
Scheme 107. *Reagents and conditions*: a. **453**, $(COCl)_2$, DMF, rt, 30 min then **421** or **427**, DMAP, THF, rt, 18 h.

Table 46. Synthesis of trimethylsilylpropiolate esters **454-455**.

Entry	Phenol	R^1	R^2	R^3	Product	Yield/%
1	**421**	Me	H	H	**454**	95
2	**427**	OMe	OMe	Me	**455**	82

Finally, IMDA reaction of trimethylsilylpropiolate ester **455** was attempted to ascertain whether the 2-trimethylsilylpyridine could be prepared for further functionalisation. In the event, heating **455** under reflux in xylene or in a sealed tube at

180 °C for 16 hours led to recovery of the starting material (**Scheme 108**). Switching to the higher boiling solvent *o*-dichlorobenzene and increasing the temperature to 220 °C was necessary to induce intramolecular cycloaddition. Loss of the trimethylsilyl group was observed during this process to afford pyridine **456** in 38% yield. Oxidation of the C-2 methyl group, opening of the lactone and functionalisation of the C-6 position with a halogen or metal atom would deliver the fully functionalised CD-rings of streptonigrin **215** suitable for cross-coupling with AB-ring fragment **317**, although this has yet to be realised.



454 **456**

Scheme 108. *Reagents and conditions*: a. *o*-dichlorobenzene, 220 °C, sealed tube, 16 h.

3.13 Conclusions and Future Work

In conclusion, the intramolecular 1-aza-Diels-Alder reaction has been presented as a versatile method for the synthesis of a variety of [*c*]-annelated pyridines. First, a series of model IMDA substrates were rapidly prepared from commercially available salicaldehydes, and then subsequently shown to undergo thermally induced cycloaddition in moderate to good yield.

This methodology was subsequently utilised in the synthesis of the penta-substituted pyridine core of the naturally occurring antibiotic streptonigrin. However, difficulties were encountered on attempted oxidation of the pyridine C-2 methyl group to the carboxylic acid present in the natural product. Activation of this methyl group by virtue of introducing an electron-withdrawing substituent in the *para*-position allowed this oxidation to be carried out in nearly quantitative yield in a related model system. Unfortunately, synthesis of the propiolate ester required for the synthesis of streptonigrin could not be achieved. However, the appropriately substituted trimethylsilylpropiolate ester was prepared in good yield, and subsequent intramolecular cycloaddition delivered a tetra-substituted pyridine which may be suitable for further elaboration into the natural product.

Chapter 4

Experimental

4.1 General Information

Commercially available reagents were used throughout without further purification unless otherwise stated; solvents were dried by standard procedures. Light petroleum refers to the fraction with bp 40-60 °C and ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen or argon atmosphere. Fully characterised compounds were chromatographically homogeneous. IR spectra were recorded in the range 4000-600 cm^{-1} using a Nicolet Magna 550 or Bruker Tensor 27 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker DRX500, AV400 or AM300 spectrometer operating at 500 MHz, 400 MHz and 300 MHz respectively (^{1}H frequency, corresponding ^{13}C frequencies are 125 MHz, 100 MHz and 75 MHz). In the ^{13}C NMR spectra, signals corresponding to CH, CH_2, or Me groups are assigned from DEPT. High and low-resolution mass spectra were recorded on a Thermoquest AS 2000 spectrometer (EI) or Bruker microTOF spectrometer (ESI). Microwave reactions were carried out in a CEM Discover™ mono-mode focused microwave reactor using an IR temperature probe.

4.2 General Procedures

General Procedure 1 - silylation of α-ketoximes

To a stirred solution of the α-ketoxime (5.0 mmol) in dry dichloromethane (10 mL) at 0 °C was added dropwise diisopropylethylamine (1.68 g, 13.0 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.30 g, 12.5 mmol). Stirring was continued at 0 °C for 2-4 h, and the solvent evaporated. The residue was diluted with *n*-pentane (25 mL), stirred at 0 °C for 1 h, then filtered and evaporated to afford the title compound, which was used without further purification.

General Procedure 2 - preparation of α-ketohydrazones

To a stirred solution of 2,3-butanedione (0.861 g, 10.0 mmol) in ethanol (10 mL) at 0 °C was added the hydrazine (11.0 mmol) dropwise. Stirring was continued at 0 °C until the reaction was judged to be complete by TLC. The solution was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound.

General Procedure 3 - silylation of α-ketohydrazones

To a stirred solution of the α-ketohydrazone (10.0 mmol) in dry dichloromethane (10 mL) at 0 °C was added dropwise diisopropylethylamine (1.68 g, 13.0 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.30 g, 12.5 mmol). Stirring was continued at 0 °C for 2 h, and the solvent evaporated. The residue was diluted with *n*-pentane (25 mL), stirred at 0 °C for 1 h, then filtered and evaporated to afford the title compound, which was used without further purification.

General procedure 4 - intermolecular hetero-Diels-Alder reactions under microwave irradiation

A solution of the 1-aza-1,3-butadiene (1.0 mmol) and the dienophile (1.0-2.0 mmol) in toluene (2 mL) in a sealed microwave tube (10 mL capacity) was irradiated at 300 W with simultaneous cooling and held at 150 °C for the time indicated. The resulting mixture was concentrated *in vacuo*, and the crude product purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:19) to afford the title compound.

General procedure 5 - intermolecular hetero-Diels-Alder reactions under microwave irradiation

A solution of the 1-aza-1,3-butadiene (1.0 mmol) and the dienophile (1.0-2.0 mmol, 1.0-2.0 equiv) in toluene (2 mL) and THF (0.25 mL) in a sealed microwave tube (10 mL capacity) was irradiated at 300 W with simultaneous cooling and held at 180 °C for the time indicated. The resulting mixture was concentrated *in vacuo*, and the crude product purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:19) to afford the title compound.

General procedure 6 - alkylation of salicaldehydes

To a solution of the salicaldehyde (10.0 mmol) in ethanol (60 mL) was added potassium carbonate (2.07 g, 15.0 mmol, 1.5 equiv) and propargyl chloride (3.62 mL, 50.0 mmol, 5.0 equiv). The reaction mixture was heated under reflux for 16 h, cooled to room temperature and the solvent removed *in vacuo*. The residue was partitioned between sodium hydroxide solution (2 M; 150 mL) and ether (3 × 150 mL). The combined organic extracts were washed with water (150 mL), dried over $MgSO_4$ and

concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:19) to afford the title compound.

General Procedure 7 - Wadsworth-Emmons reactions

To a solution of sodium hydride (0.360 g, 9.00 mmol, 1.5 equiv) or potassium *tert*-butoxide (1.01 g, 9.00 mmol, 1.5 equiv) in 1,2-dimethoxyethane (10 mL) was added the phosphonate (9.00 mmol, 1.5 equiv) in 1,2-dimethoxyethane (5 mL) dropwise over 30 min. The reaction mixture was stirred for 30 min, followed by dropwise addition of the aldehyde (6.00 mmol) in 1,2-dimethoxyethane (5 mL) over 30 min. The resulting mixture was stirred at room temperature for 16 h and partitioned between saturated ammonium chloride (75 mL) and ethyl acetate (3 × 75 mL). The combined organic extracts were washed with water (75 mL) and saturated brine (75 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9), to afford the title compound.

General Procedure 8 - Sonagashira reactions

To a solution of the aryl iodide (3.33 mmol), bis(triphenylphosphine)palladium (II) chloride (0.164 g, 0.233 mmol, 7 mol%) and copper (I) iodide (0.190 g, 1.00 mmol, 0.3 equiv) in THF (35 mL) was added triethylamine (0.70 mL, 5.00 mmol, 1.5 equiv), followed by the alkyne (5.00 mmol, 1.5 equiv) in THF (15 mL). The reaction mixture was heated at 60 °C for 18 h, then partitioned between saturated ammonium chloride (75 mL) and ethyl acetate (3 × 75 mL). The combined organics were washed with saturated ammonium chloride (2 × 75 mL) and saturated brine (75 mL), dried over

$MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9 to 1:3) to afford the title compound.

General Procedure 9 - preparation of *O*-methyl oximes

A solution of the ketone (4.00 mmol), methoxylamine hydrochloride (0.418 g, 5.00 mmol, 1.25 equiv) and sodium acetate trihydrate (0.455 g, 4.20 mmol, 1.05 equiv) in ethanol (28 mL) and water (3.5 mL) was heated to 60 °C for 16 h. The reaction mixture was cooled to room temperature and the solvent removed *in vacuo*. The resulting residue was partitioned between water (65 mL) and ethyl acetate (3 × 65 mL). The combined organic extracts were washed with water (2 × 65 mL) and saturated brine (65 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound which was used without further purification.

General Procedure 10 - functionalisation of terminal alkynes

To a solution of the *O*-methyl oxime (4.00 mmol) in THF (10 mL) at -78 °C was added lithium hexamethyldisilazide (1 M in THF; 4.20 mL, 4.20 mmol, 1.05 equiv) dropwise over 20 min. The reaction mixture was stirred at -78 °C for 1 h, then the electrophile (6.00 mmol, 1.5 equiv) added dropwise over 15 min. The resulting mixture was then stirred for a further 1 h at -78 °C, allowed to warm to room temperature and stirred for 16 h. The reaction was quenched by addition of saturated ammonium chloride (75 mL), and the aqueous phase extracted with ethyl acetate (3 × 75 mL). The combined organic extracts were washed with water (75 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound.

General Procedure 11 - intramolecular hetero-Diels-Alder reactions

A solution of the α,β-unsaturated oxime (0.50 mmol) in dry xylene (10 mL) was placed in a sealed tube and heated to the required temperature for the time indicated. The reaction mixture was then cooled to room temperature, concentrated *in vacuo* and the crude product purified by flash chromatography on silica gel to afford the title compound.

General Procedure 12 - one-pot oxime formation/intramolecular hetero-Diels-Alder reaction

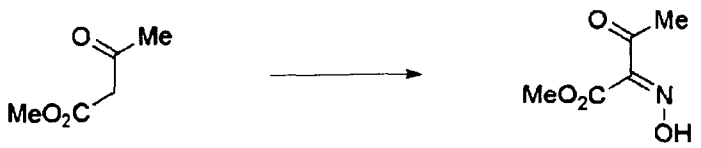
A solution of the α,β-unsaturated oxime (0.50 mmol), methoxylamine hydrochloride (0.084 g, 1.00 mmol, 2.00 equiv) and triethylamine (0.139 mL, 1.00 mmol, 2.00 equiv) in xylene (10 mL) in a sealed tube was heated at 180 °C for 16 h. The reaction mixture was cooled to room temperature and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the *title compound.*

General Procedure 13 - acylation of diethyl ethylphosphonate

To a stirred solution of *n*-butyllithium (2.5 M in hexanes; 26.5 mL, 66.2 mmol, 1.10 equiv) in THF (50 mL) at -78 °C was added diethyl ethylphosphonate (10.0 g, 60.2 mmol) in THF (15 mL) dropwise over 30 min. Stirring was continued at -78 °C for 1 h. The electrophile (66.2 mmol, 1.10 equiv) in THF (15 mL) was added dropwise over 10 min. After a further 1 h at -78 °C, the reaction mixture was allowed to warm slowly to room temperature and stirred for 16 h. The reaction was quenched by the addition of citric acid (10%, 150 mL) and the aqueous phase was then extracted with dichloromethane (2 × 250 mL). The combined organics were washed with saturated

brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:1 to 4:1) to afford the title compound.

Methyl oximinoacetoacetate[89] 233



233

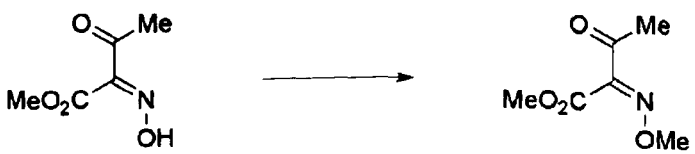
To a stirred solution of methyl acetoacetate (11.60 g, 0.100 mol) in acetic acid (14.3 mL) at -5 °C was added sodium nitrite (7.72 g, 0.112 mol) in water (20 mL). The reaction mixture was allowed to warm to room temperature and stirred for 30 min. Water (60 mL) was added and stirring continued for 2.5 h. The reaction mixture was then extracted with ether (3 × 40 mL) and the combined organics washed with water (20 mL), saturated sodium hydrogen carbonate solution (4 × 20 mL) and water (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a colourless oil (13.20 g, 91%); ν_{max} ($CHCl_3$)/cm^{-1} 3363 (O-H), 3034 (O-H), 1748 (C=O), 1694 (C=O), 1627 (C=N); δ_H (300 MHz; $CDCl_3$) 9.55 (1 H, br s, OH), 3.90 (3 H, s, OMe), 2.42 (3 H, s, Me); δ_C (75 MHz; $CDCl_3$) 195.0 (C), 162.9 (C), 151.3 (C), 55.4 (OMe), 25.7 (Me).

2,3-Butanedione mono(*O*-methyl-oxime)[200] 234

232 234

To 2,3-butanedione monoxime (2.02 g, 20.0 mmol) was added 10% sodium hydroxide (8.8 mL, 22.0 mmol). Dimethyl sulfate (3.03 g, 24.0 mmol) was added dropwise, during which the temperature increased to ca. 40 °C. The reaction mixture was stirred for 30 min, then refluxed for 5 min. The reaction mixture was then separated and the aqueous phase extracted with ether (2 × 20 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a colourless oil (1.79 g, 78%), which may be distilled to purity *in vacuo* (0.807 g, 35%); ν_{max} (film)/cm^{-1} 1694 (C=O), 1609 (C=N); δ_H (300 MHz; $CDCl_3$) 4.06 (3 H, s, OMe), 2.37 (3 H, s, Me), 1.91 (3 H, s, Me); δ_C (75 MHz; $CDCl_3$) 197.0 (C), 155.8 (C), 63.4 (OMe), 25.2 (Me), 8.8 (Me).

2-(Methoxyimino)-3-oxo-butanoic acid methyl ester[201] 235

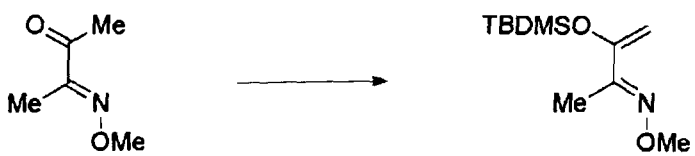


233 235

To a stirred suspension of methyl oximinoacetoacetate (1.45 g, 10.0 mmol) and potassium carbonate (2.07 g, 15.0 mmol) in acetone (15 mL) at 10 °C was added dropwise dimethyl sulfate (1.26 g, 10.0 mmol). The reaction mixture was stirred at 4 °C for 24 h, poured into water (50 mL) and extracted with CH_2Cl_2 (4 × 50 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a colourless oil (1.41 g, 89%), which was used without further

purification; (Found: M^+, 159.0519. $C_6H_9NO_4$ requires 159.0532); ν_{max} ($CHCl_3$)/cm^{-1} 1748 (C=O), 1602 (C=N); δ_H (300 MHz; $CDCl_3$) 4.11 (3 H, s, OMe), 3.88 (3 H, s, OMe), 2.41 (3 H, s, Me); *m/z* (EI) 172 (9%), 158 (7), 149 (11), 144 (26), 116 (49), 113 (18), 86 (78), 59 (100).

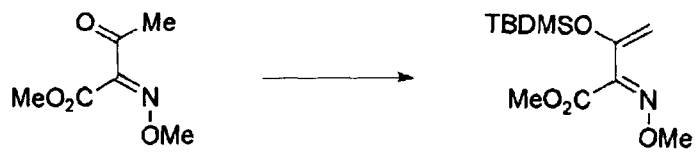
3-(*tert*-Butyldimethylsilyloxy)-but-3-en-2-one *O*-methyl-oxime 236



234 **236**

Following general procedure 1, the title compound was obtained from 2,3-butanedione mono-(*O*-methyl oxime) **234** (0.576 g, 5.00 mmol), then purified by flash chromatography on silica gel to afford the *title compound* as a colourless oil (0.950 g, 83%), containing 1,3-di-*tert*-butyl-1,1,3,3-tetramethyl-disiloxane (0.130 g); (Molecular ion not found. $C_{11}H_{23}NO_2Si$ requires 229.1498); ν_{max} (film)/cm^{-1} 1619 (C=C), 1254 (Si-Me), 1059 (Si-O); δ_H (300 MHz; $CDCl_3$) 4.78 (1 H, d, J = 1.1 Hz, C=CH), 4.50 (1 H, d, J = 1.1 Hz, C=CH), 3.92 (3 H, s, OMe), 1.92 (3 H, s, Me), 0.95 (9 H, s, CMe_3), 0.17 (6 H, s, $SiMe_2$); δ_C (75 MHz; $CDCl_3$) 153.7 (C), 153.4 (C), 96.7 (CH_2), 62.3 (OMe), 26.1 (Me), 18.7 ($\underline{C}Me_3$), 11.5 (Me), -2.6 ($SiMe_2$). *m/z* (EI) 285 (23%), 266 (22), 190 (40), 172 (43), 147 (11), 127 (8), 121 (100), 115 (25), 113 (15), 89 (12), 84 (18), 72 (30), 69 (96), 58 (30).

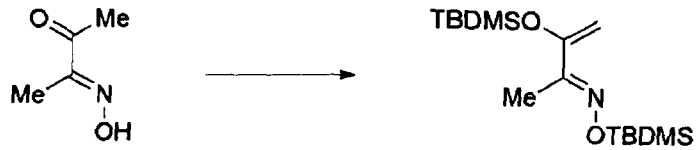
3-(*tert*-Butyldimethylsilyloxy)-2-(methoxyimino)-but-3-enoic acid methyl ester 237



235 **237**

To a stirred solution of 2-(methoxyimino)-3-oxo-butanoic acid methyl ester **235** (1.20 g, 7.34 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C was added dropwise diisopropylethylamine (1.27 g, 9.80 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.49 g, 9.43 mmol). Stirring was continued at 0 °C for 2.5 h, then further base (0.508 g, 4.90 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.25 g, 4.72 mmol) added. Stirring was continued for 3 h then further base (0.508 g, 4.90 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.25 g, 4.72 mmol) added. Stirring was continued for 1.5 h and the solvent evaporated. The residue was diluted with *n*-pentane (50 mL), stirred at 0 °C for 1.5 h, then filtered and evaporated. The crude material was purified by flash chromatography on silica gel, eluting with dichloromethane to afford the *title compound* as a colourless oil (1.11 g, 54%); (Found: MH^+, 274.1476. $C_{12}H_{23}NO_4Si$ + H requires 274.1474); ν_{max} (film)/cm^{-1} 1748 (C=O), 1614 (C=C), 1259 (Si-Me), 1047 (Si-O); δ_H (300 MHz; $CDCl_3$) 4.67 (2 H, s, CH_2), 3.95 (3 H, s, OMe), 3.85 (3 H, s, OMe), 0.94 (9 H, s, CMe_3), 0.19 (6 H, s, $SiMe_2$); δ_C (75 MHz; $CDCl_3$) 163.8 (C), 149.8 (C), 148.9 (C), 100.0 (CH_2), 63.5 (OMe), 52.8 (OMe), 26.0 (Me), 18.6 ($\underline{C}Me_3$), -3.2 ($SiMe_2$); *m/z* (EI) 232 (10%), 218 (100), 216 (54), 200 (28), 188 (12), 172 (13), 158 (23), 146 (40), 129 (15), 116 (18), 100 (22), 86 (53), 84 (60), 73 (91), 59 (96).

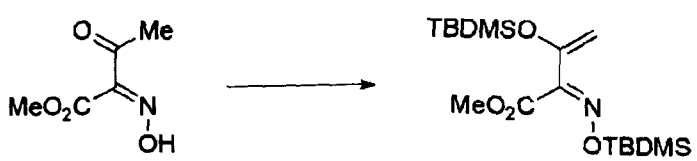
2-Methyl-1,3-bis(*tert*-butyldimethylsiloxy)-1-aza-1,3-butadiene 238



232 **238**

Following general procedure 1, the *title compound* was obtained from 2,3-butanedione monoxime (0.435 g, 5.0 mmol) as a colourless oil (1.44 g, 87%); (Found: MH^+, 330.2281. $C_{16}H_{35}NO_2Si_2$ + H requires 330.2284); ν_{max} (film)/cm^{-1} 1615 (C=C), 1254 (Si-Me), 1030 (Si-O); δ_H (300 MHz; $CDCl_3$) 4.78 (1 H, d, J = 1.1 Hz, C=CH), 4.48 (1 H, d, J = 1.1 Hz, C=CH), 1.96 (3 H, s, Me), 0.94 (9 H, s, CMe_3), 0.92 (9 H, s, CMe_3), 0.16 (6 H, s, $SiMe_2$), 0.14 (6 H, s, $SiMe_2$); δ_C (75 MHz; $CDCl_3$) 158.2 (C), 154.1 (C), 96.6 (CH_2), 26.5 (Me), 26.1 (Me), 18.6 ($\underline{C}Me_3$), 18.4 ($\underline{C}Me_3$), 11.6 (Me), -4.1 ($SiMe_2$), -4.3 ($SiMe_2$); *m/z* (CI) 358 (15%), 330 (MH^+, 90), 314 (100), 272 (85), 231 (37), 216 (13), 200 (18), 189 (30), 156 (12), 115 (21).

2-Methoxycarbonyl-1,3-bis(*tert*-butyldimethylsiloxy)-1-aza-1,3-butadiene 239

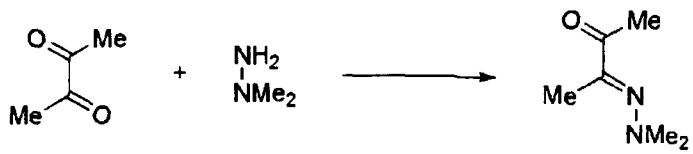


233 **239**

Following general procedure 1, the *title compound* was obtained from **233** (0.716 g, 5.0 mmol) as a colourless oil (1.73 g, 93%); (Found: MH^+, 374.2182. $C_{17}H_{35}NO_4Si_2$ + H requires 374.2183); ν_{max} (film)/cm^{-1} 1751 (C=O), 1614 (C=C), 1254 (Si-Me), 1102 (Si-O); δ_H (300 MHz; $CDCl_3$) 4.68 (1 H, d, J = 2.1 Hz, C=CH), 4.64 (1 H, d, J = 2.1 Hz, C=CH), 3.83 (3 H, s, OMe), 0.94 (9 H, s, CMe_3), 0.89 (9 H, s, CMe_3), 0.16 (12 H, s, 2 × $SiMe_2$); δ_C (75 MHz; $CDCl_3$) 164.3 (C), 155.2 (C), 149.1 (C), 100.3 (CH_2), 52.4

(Me), 26.1 (Me), 26.0 (Me), 18.5 ($\underline{C}Me_3$), 18.3 ($\underline{C}Me_3$), -4.3 ($SiMe_2$), -5.0 ($SiMe_2$); *m/z* (CI) 402 (8%), 374 (MH^+, 32), 358 (50), 316 (60), 286 (10), 247 (18), 231 (90), 200 (10), 189 (100), 184 (20), 157 (40), 147 (50), 115 (70), 86 (100), 73 (28).

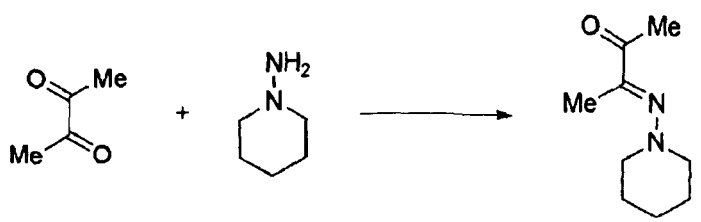
2,3-Butanedione mono(dimethylhydrazone)[50] 248



242 **243** **248**

Following general procedure 2, the title compound was obtained from 2,3-butanedione **242** (8.61 g, 0.100 mol) as a yellow oil (9.17 g, 72%); ν_{max} ($CHCl_3$)/cm^{-1} 1672 (C=O); δ_H (300 MHz; $CDCl_3$) 2.96 (6 H, s, NMe_2), 2.32 (3 H, s, Me), 2.01 (3 H, s, Me); δ_C (75 MHz; $CDCl_3$) 199.4 (C), 147.6 (C), 47.3 (NMe_2), 24.8 (Me), 13.2 (Me).

3-(Piperidin-1-ylimino)-butan-2-one 249



242 **244** **249**

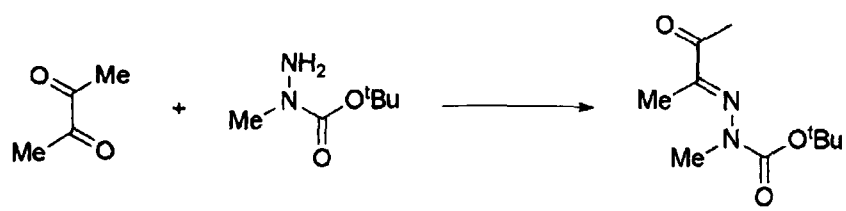
Following general procedure 2, the *title compound* was obtained from 1-aminopiperidine (1.10 g, 11.0 mmol) as a colourless oil (1.02 g, 62%); (Found: MH^+, 169.1363. $C_9H_{16}N_2O$ + H requires 169.1341); ν_{max} (film)/cm^{-1} 1687 (C=O); δ_H (300 MHz; $CDCl_3$) 3.12 - 3.08 (4 H, m, 2 × CH_2), 2.35 (3 H, s, Me), 1.98 (3 H, s, Me), 1.74 - 1.67 (4 H, m, 2 × CH_2), 1.59 - 1.54 (2 H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 199.7 (C), 152.4 (C), 55.9 (CH_2), 25.7 (CH_2), 24.9 (Me), 24.4 (CH_2), 13.6 (Me); *m/z* (CI) 197 (8%), 169 (MH^+, 100), 84 (15).

_N_-Methyl-hydrazinecarboxylic acid _tert_-butyl ester[202] 245

245

To a stirred solution of methyl hydrazine (0.461 g, 10.0 mmol) and DMAP (37.0 mg, 0.300 mmol) in acetonitrile (10 mL) was added dropwise di-*tert*-butyl dicarbonate (2.40 g, 11.0 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature overnight and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate/light petroleum (1:3) to afford the title compound as a colourless oil (1.34 g, 92%); ν_{max} (film)/cm^{-1} 3334 (NH_2), 3221 (NH_2), 1694 (C=O); δ_H (300 MHz; $CDCl_3$) 4.10 (2 H, br s, NH_2), 3.06 (3 H, s, Me), 1.48 (9 H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 80.8 ($\underline{C}Me_3$), 38.6 (Me), 28.8 (Me).

_N_-Methyl-_N'_-[1-methyl-2-oxo-propylidene]-hydrazinecarboxylic acid _tert_-butyl ester 250



242 **245** **250**

Following general procedure 2, the *title compound* was obtained from 2,3-butanedione **242** (0.430 g, 5.00 mmol) and *N*-methyl-hydrazinecarboxylic acid *tert*-butyl ester **245** (0.805 g, 5.50 mmol) as a colourless oil (1.03 g, 96%); (Found: MH^+, 215.1388. $C_{10}H_{18}N_2O_3$ + H requires 215.1395); ν_{max} (film)/cm^{-1} 1699 (C=O), 1610 (C=N); δ_H (300 MHz; $CDCl_3$) 3.29 (3 H, s, NMe), 2.44 (3 H, s, Me), 1.95 (3 H, s, Me), 1.50 (9 H,

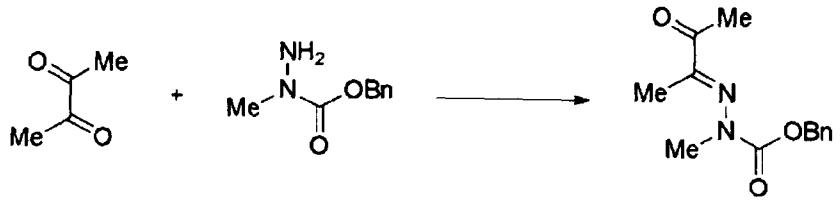
s, CMe_3); δ_C (75 MHz; $CDCl_3$) 199.4 (C), 163.7 (C), 152.5 (C), 82.1 ($\underline{C}Me_3$), 39.4 (Me), 28.7 (Me), 25.5 (Me), 14.6 (Me); *m/z* (CI) 215 (MH^+, 20%), 187 (30), 159 (100), 143 (15), 115 (92).

1-Benzyloxycarbonyl-1-methyl-hydrazine[203] 246

246

To a stirred solution of methylhydrazine (0.461 g, 10.0 mmol) in dry dichloromethane (20 mL) at 0 °C was added triethylamine (1.21 g, 12.0 mmol) and benzyl chloroformate (1.88 g, 11.0 mmol). The reaction was allowed to warm to room temperature and stirred for 2 h. Water (15 mL) was added, and the organic layer separated. The aqueous layer was further extracted with dichloromethane (3 × 25 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:1) to afford the title compound as a colourless oil (1.04 g, 58%); ν_{max} ($CHCl_3$)/cm^{-1} 3026 (NH_2), 1697 (C=O), 1627 (C=C), 1498 (C=C); δ_H (300 MHz; $CDCl_3$) 7.38 - 7.31 (5 H, m, ArH), 5.15 (2 H, s, CH_2), 3.82 (2 H, br s, NH_2), 3.14 (3 H, s, Me); δ_C (75 MHz; $CDCl_3$) 136.8 (C), 129.0 (CH), 128.6 (CH), 128.5 (CH), 68.1 (CH_2), 38.8 (Me).

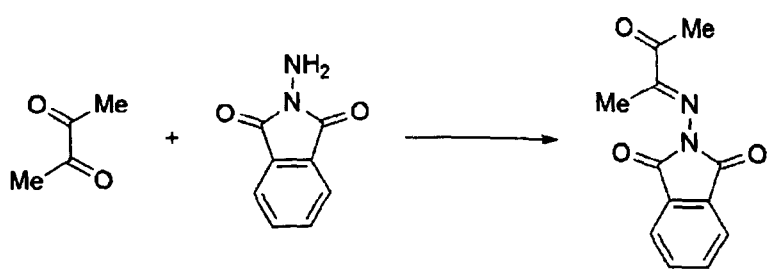
_N_-Benzyloxycarbonyl-_N_-methyl butane-2,3-dione monohydrazone 251



242 **246** **251**

Following general procedure 2, the *title compound* was obtained from 1-methyl-1-benzyloxycarbonylhydrazine **246** (0.991 g, 5.5 mmol) as a colourless solid (0.963 g, 78%), mp 64-65 °C (from light petroleum); (Found: MH^+, 249.1236. $C_{13}H_{16}N_2O_3$ + H requires 249.1239); ν_{max} ($CHCl_3$)/cm^{-1} 1703 (C=O), 1613 (C=N), 1469 (C=C); δ_H (300 MHz; $CDCl_3$) 7.39 - 7.32 (5 H, m, ArH), 5.21 (2 H, s, CH_2), 3.35 (3 H, s, NMe), 2.44 (3 H, s, Me), 1.95 (3 H, s, Me); δ_C (75 MHz; $CDCl_3$) 199.2 (C), 164.8 (C), 153.6 (C), 136.3 (C), 129.0 (CH), 128.8 (CH), 128.5 (CH), 68.5 (CH_2), 39.3 (Me), 25.6 (Me), 14.6 (Me); *m/z* (CI) 339 (30%), 249 (MH^+, 100), 205 (25), 181 (10), 137 (10), 91 (48).

_N_-Phthaloyl butane-2,3-dione monohydrazone[93] 252

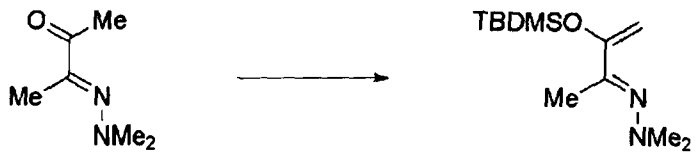


242 **247** **252**

To a stirred solution of 2,3-butanedione **242** (8.61 g, 0.100 mol) in chloroform (200 mL) was added *N*-aminophthalimide **247** (17.8 g, 0.110 mol). The reaction mixture was heated under reflux for 3 d, allowed to cool to room temperature, filtered and concentrated *in vacuo* to afford the title compound as a colourless solid (20.1 g, 87%), mp 157-158 °C (from chloroform), (lit., mp 165 °C), which was used without further

purification; δ_H (300 MHz; $CDCl_3$) 7.95 - 7.92 (2 H, m, ArH), 7.82 - 7.79 (2 H, m, ArH), 2.60 (3 H, s, Me), 2.11 (3 H, s, Me); δ_C (75 MHz; $CDCl_3$) 198.0 (C), 172.1 (C), 163.6 (C), 135.1 (CH), 131.4 (C), 124.4 (CH), 26.0 (Me), 16.1 (Me).

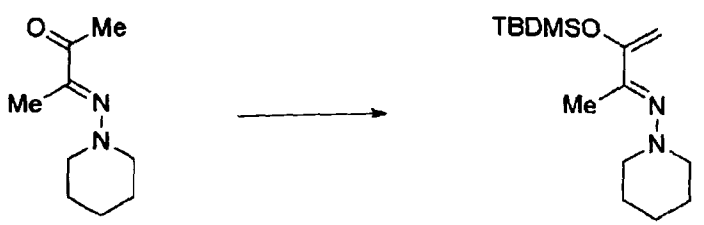
3-(*tert*-Butyldimethylsiloxy)-2-methyl-1-(dimethylamino)-1-aza-1,3-butadiene[50] 53



248 **53**

Following general procedure 3, the title compound was obtained from 2,3-butanedione mono(dimethylhydrazone) **248** (1.92 g, 15.0 mmol) as a colourless oil (3.47 g, 95%); ν_{max} ($CHCl_3$)/cm^{-1} 1616 (C=N), 1593 (C=C), 1254 (Si-Me), 1228 (NMe_2), 1204 (NMe_2); δ_H (400 MHz; $CDCl_3$) 4.87 (1 H, d, J = 1.2 Hz, C=CH), 4.51 (1 H, d, J = 1.2 Hz, C=CH), 2.55 (6 H, s, $N(CH_3)_2$), 2.05 (3 H, s, CH_3), 0.96 (9 H, s, $C(CH_3)_3$), 0.18 (6 H, s, $Si(CH_3)_2$); δ_C (100 MHz; $CDCl_3$) 157.7 (C), 153.6 (C), 94.2 (CH_2), 45.1 (NMe_2), 23.6 ($C\underline{Me}_3$), 16.3 ($\underline{C}Me_3$), 12.2 (Me).

3-(*tert*-Butyldimethylsiloxy)-2-methyl-1-(piperidinyl)-1-aza-1,3-butadiene 253

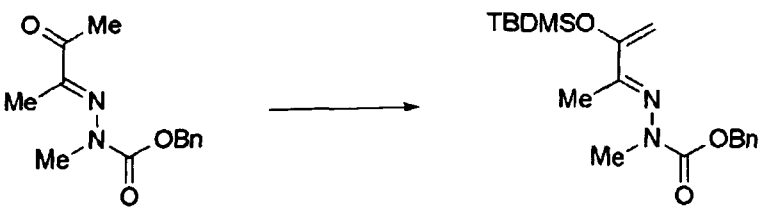


249 **253**

Following general procedure 3, the *title compound* was obtained from 3-(piperidin-1-ylimino)-butan-2-one **249** (0.504 g, 3.0 mmol) as a colourless oil (0.715 g, 84%); (Found: MH^+, 283.2205. $C_{15}H_{30}N_2OSi$ + H requires 283.2205); ν_{max} ($CHCl_3$)/cm^{-1}

1615 (C=N), 1593 (C=C), 1253 (Si-Me); δ_H (300 MHz; $CDCl_3$) 4.86 (1 H, d, J = 0.9 Hz, C=CH), 4.52 (1 H, d, J = 0.9 Hz, C=CH), 2.75 - 2.71 (4 H, m, 2 × CH_2), 2.04 (3 H, s, Me), 1.72-1.65 (4 H, m, 2 × CH_2), 1.48-1.44 (2 H, m, CH_2), 0.96 (9 H, s, CMe_3), 0.17 (6 H, s, $SiMe_2$); δ_C (75 MHz; $CDCl_3$) 160.4 (C), 156.2 (C), 96.9 (CH_2), 56.5 (CH_2), 26.2 (CH_2), 25.7 (CH_2), 24.3 (CH_2), 18.8 ($\underline{C}Me_3$), 14.8 (Me), -2.5 ($SiMe_2$); *m/z* 311 (8%), 283 (MH^+, 100), 267 (45), 225 (30), 200 (5), 169 (10), 159 (5).

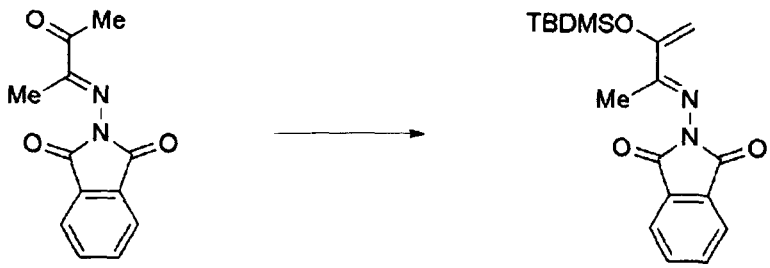
1-(Benzyloxycarbonylmethylamino)-*3*-(*tert*-butyldimethylsiloxy)-2-methyl-1-aza-1,3-butadiene 255



251 **255**

Following general procedure 3, the *title compound* was obtained from *N*-benzyloxycarbonyl-*N*-methyl butane-2,3-dione monohydrazone **251** (0.745 g, 3.0 mmol) as a colourless oil (1.01 g, 93%); (Found: MH^+, 363.2097. $C_{19}H_{30}N_2O_3Si$ + H requires 363.2104); ν_{max} ($CHCl_3$)/cm^{-1} 1698 (C=O), 1620 (C=N), 1595 (C=C), 1498 (C=C), 1472 (C=C), 1256 (Si-Me); δ_H (300 MHz; $CDCl_3$) 7.35 - 7.32 (5 H, m, ArH), 5.15 (2 H, s, CH_2), 5.04 (1 H, d, J = 1.3 Hz, C=CH), 4.60 (1 H, d, J = 1.3 Hz, C=CH), 3.20 (3 H, s, NMe), 1.93 (3 H, s, Me), 0.95 (9 H, s, CMe_3), 0.16 (6 H, s, $SiMe_2$); δ_C (75 MHz; $CDCl_3$) 178.0 (C), 163.5 (C), 154.7 (C), 136.8 (C), 128.9 (CH), 128.5 (CH), 128.4 (CH), 98.7 (CH_2), 67.9 (CH_2), 38.1 (Me), 26.1 (Me), 16.0 ($\underline{C}Me_3$), 14.5 (Me), -2.5 ($SiMe_2$); *m/z* (CI) 453 (8%), 363 (MH^+, 25), 339 (8), 311 (10), 283 (80), 271 (22), 249 (12), 221 (20), 193 (57), 181 (25), 149 (27), 137 (18), 91 (100).

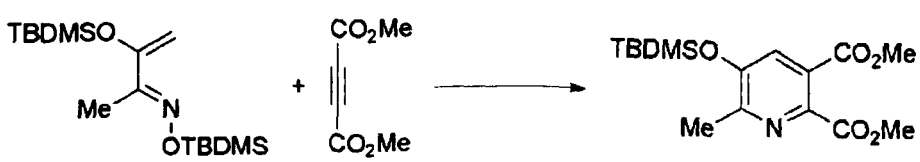
3-(*tert*-Butyldimethylsiloxy)-2-methyl-1-(phthalimido)-1-aza-1,3-butadiene 256



252 **256**

Following general procedure 3, the *title compound* was obtained from *N*-phthaloyl butane-2,3-dione monohydrazone **252** (1.15 g, 5.0 mmol) as a colourless solid (1.38 g, 79%), mp 106-107 °C (from ethanol); (Found: MH^+, 345.1632. $C_{18}H_{24}N_2O_3Si$ + H requires 345.1634); ν_{max} ($CHCl_3$)/cm^{-1} 1717 (C=O), 1618 (C=N), 1596 (C=C), 1467 (C=C), 1256 (Si-Me); δ_H (300 MHz; $CDCl_3$) 7.89 - 7.86 (2 H, m, ArH), 7.76 - 7.73 (2 H, m, ArH), 5.30 (1 H, d, J = 1.3 Hz, C=CH), 4.75 (1 H, d, J = 1.3 Hz, C=CH), 2.07 (3 H, s, Me), 1.00 (9 H, s, CMe_3), 0.23 (6 H, s, $SiMe_2$); δ_C (75 MHz; $CDCl_3$) 174.0 (C), 164.3 (C), 153.8 (C), 134.6 (CH), 131.6 (C), 124.0 (CH), 100.3 (CH_2), 26.1 (Me), 18.7 ($\underline{C}Me_3$), 17.5 (Me), - 4.7 ($SiMe_2$); *m/z* (CI) 373 (10%), 345 (MH^+, 95), 287 (50), 200 (32), 148 (100).

Dimethyl 5-(*tert*-butyldimethylsiloxy)-6-methylpyridine-2,3-dicarboxylate 240



238 **136** **240**

a) Following general procedure 4 from **238** (0.330 g, 1.0 mmol) and DMAD **136** (0.284 g, 2.0 mmol), the *title compound* was obtained in 6 h as a colourless oil (0.190 g, 56%); (Found: M^+, 339.1507. $C_{16}H_{25}NO_5Si$ requires 339.1502); ν_{max} (film)/cm^{-1} 1732 (C=O), 1588 (C=C), 1558 (C=C), 1461 (C=C),1258 (Si-Me); δ_H (300 MHz;

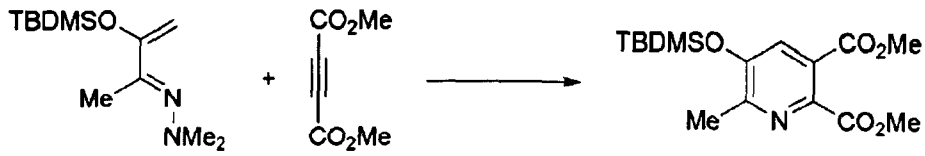
$CDCl_3$) 7.35 (1 H, s, H-4), 3.95 (3 H, s, OMe), 3.90 (3 H, s, OMe), 2.52 (3 H, s, Me), 1.00 (9 H, s, CMe_3), 0.25 (6 H, s, $SiMe_2$); δ_C (75 MHz; $CDCl_3$) 167.1 (C), 166.5 (C), 155.0 (C), 151.8 (C), 142.0 (C), 126.4 (C), 125.0 (CH), 53.4 (Me), 53.3 (Me), 26.2 (Me), 20.5 (Me), 18.6 ($\underline{C}Me_3$), -3.9 ($SiMe_2$); *m/z* (EI) 339 (M^+, 12%), 308 (8), 282 (36), 250 (100), 222 (18), 192 (28), 164 (20).

b) Following general procedure 4 from **238** (0.330 g, 1.0 mmol) and DMAD (0.142 g, 1.0 mmol), the title compound was obtained in 8 h as a colourless oil (0.170 g, 50%); data as above.

c) Following general procedure 5 from **238** (0.330 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol), the title compound was obtained in 2 h as a colourless oil (0.190 g, 56%); data as above.

d) Following general procedure 5 from **238** (0.330 g, 1.0 mmol) and DMAD (0.142 g, 1.0 mmol), the title compound was obtained in 3 h as a colourless oil (0.170 g, 50%); data as above.

e) A solution of 1-azadiene **238** (0.330 g, 1.0 mmol) and DMAD (**5**, 0.284 g, 2.0 mmol) in toluene (2 mL) in a sealed tube was heated to 150 °C for 6 h. The resulting mixture was concentrated *in vacuo* and the crude product purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:19) to afford the title compound as a colourless oil (0.194 g, 57%); data as above.

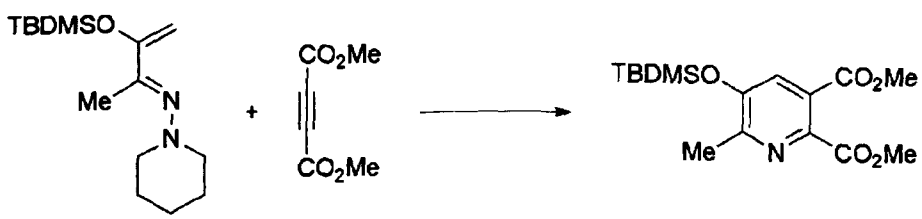


53 **136** **240**

f) Following general procedure 4 from **53** (0.242 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol), the title compound was obtained in 2 h as a colourless oil (0.176 g, 52%); data as above.

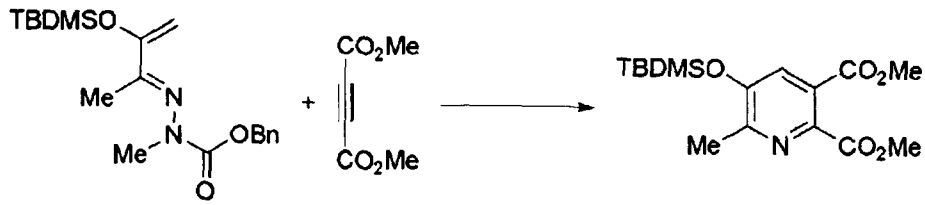
g) Following general procedure 5 from **53** (0.242 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol), the title compound was obtained in 45 min as a colourless oil (0.150 g, 44%); data as above.

h) A solution of 1-azadiene **53** (0.242 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol) in toluene (2 mL) in a sealed tube was heated to 150 °C for 2 h. The resulting mixture was concentrated *in vacuo* and the crude product purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:19) to afford the title compound as a colourless oil (0.157 g, 46%); data as above.



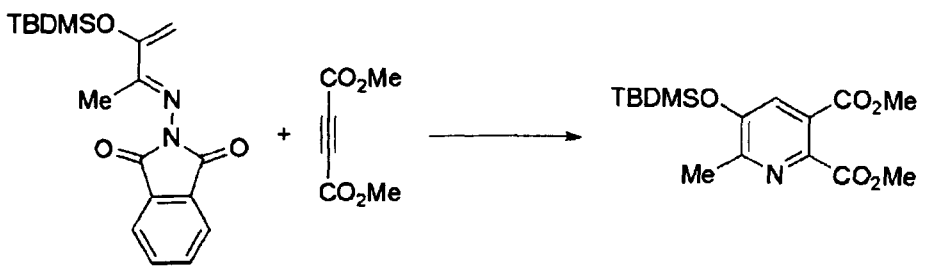
253 **136** **240**

i) Following general procedure 4 from **253** (0.283 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol), the title compound was obtained in 2 h as a colourless oil (0.160 g, 47%); data as above.



255 **136** **240**

j) Following general procedure 4 from **255** (0.363 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol), the title compound was obtained in 4 h as a colourless oil (0.157 g, 46%); data as above.

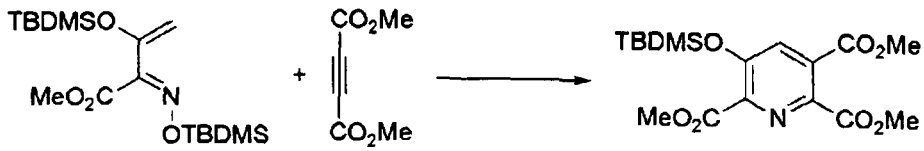


256 **136** **240**

k) Following general procedure 5 from **256** (0.344 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol), the title compound was obtained in 3 h as a colourless oil (0.197 g, 58%); data as above.

l) Following general procedure 5 from **256** (0.344 g, 1.0 mmol) and DMAD (0.142 g, 1.0 mmol), the title compound was obtained in 4 h as a colourless oil (0.183 g, 54%); data as above.

Trimethyl 5-(*tert*-butyldimethylsiloxy)pyridine-2,3,6-tricarboxylate 241

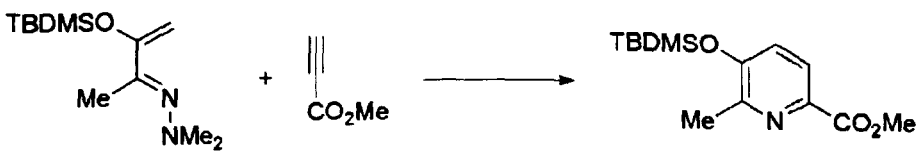


239 **136** **241**

a) Following general procedure 4 from **239** (0.374 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol), the *title compound* was obtained in 10 h as a colourless oil (0.121 g, 32%); (Found: M^+, 384.1473. $C_{17}H_{25}NO_7Si$ + H requires 384.1478); ν_{max} ($CHCl_3$)/cm^{-1} 1742 (C=O), 1589 (C=C), 1555 (C=C), 1253 (Si-Me); δ_H (300 MHz; $CDCl_3$) 7.48 (1 H, s, H-4), 3.92 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.90 (3 H, s, OMe), 0.96 (9 H, s, CMe_3), 0.25 (6 H, s, $SiMe_2$); δ_C (75 MHz; $CDCl_3$) 165.9 (C), 165.7 (C), 164.7 (C), 152.7 (C), 144.0 (C), 141.4 (C), 131.3 (C), 128.7 (CH), 53.6 (Me), 53.5 (Me), 53.2 (Me), 25.7 (Me), 18.6 ($\underline{C}Me_3$), - 3.8 ($SiMe_2$); *m/z* (CI) 384 (MH^+, 6%), 270 (100), 238 (23).

b) Following general procedure 5 from **239** (0.374 g, 1.0 mmol) and DMAD (0.284 g, 2.0 mmol), the title compound was obtained in 6 h as a colourless oil (0.119 g, 31%); data as above.

Methyl 3-(*tert*-butyldimethylsiloxy)-2-methylpyridine-6-carboxylate 258

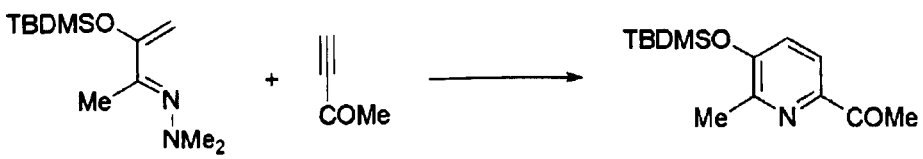


53 **228** **258**

Following general procedure 5 from **53** (0.242 g, 1.0 mmol) and methyl propiolate **228** (0.168 g, 2.0 mmol), the *title compound* was obtained in 6 h as a colourless oil (0.082 g, 29%); (Found: M^+, 282.1526. $C_{14}H_{23}NO_3Si$ requires 282.1525); ν_{max} (film)/cm^{-1} 1719 (C=O), 1574 (C=C), 1463 (C=C), 1258 (Si-Me); δ_H (300 MHz; $CDCl_3$) 7.88 (1

H, d, J = 8.3 Hz, ArH), 7.06 (1 H, d, J = 8.3 Hz, ArH), 3.92 (3 H, s, OMe), 3.51 (3 H, s, Me), 0.98 (9 H, s, CMe_3), 0.22 (6 H, s, $SiMe_2$); δ_C (75 MHz; $CDCl_3$) 168.3 (C), 156.0 (C), 154.4 (C), 142.1 (C), 127.2 (CH), 127.0 (CH), 55.5 (Me), 28.2 (Me), 22.8 (Me), 20.8 ($\underline{C}Me_3$), -1.3 ($SiMe_2$); *m/z* (CI) 282 (M^+, 100%).

6-Acetyl-3-(*tert*-butyldimethylsiloxy)-2-methylpyridine 259



53 **229** **259**

Following general procedure 5 from **53** (0.242 g, 1.0 mmol) and 3-butyn-2-one **229** (0.136 g, 2.0 mmol), the *title compound* was obtained in 6 h as a colourless oil (0.073 g, 28%); (Found: MH^+, 266.1585. $C_{14}H_{23}NO_2Si$ requires 266.1576); ν_{max} ($CHCl_3$)/cm^{-1} 1684 (C=O), 1596 (C=C), 1569 (C=C), 1508 (C=C), 1256 (Si-Me); δ_H (300 MHz; $CDCl_3$) 7.83 (1 H, d, J = 8.3 Hz, ArH), 7.07 (1 H, d, J = 8.3 Hz, ArH), 2.66 (3 H, s, Me), 2.49 (3 H, s, Me), 1.02 (9 H, s, CMe_3), 0.25 (6 H, s, $SiMe_2$); δ_C (75 MHz; $CDCl_3$) 199.9 (C), 153.8 (C), 150.7 (C), 146.6 (C), 124.7 (CH), 121.5 (CH), 26.0 (Me), 20.5 (Me), 18.6 ($\underline{C}Me_3$), -3.5 ($SiMe_2$); *m/z* (CI) 266 (MH^+, 100%), 152 (5).

Toluene-4-sulfonic acid but-3-ynyl ester[95] 265

265

A solution of *para*-toluenesulfonyl chloride (42.6 g, 0.222 mol) in warm pyridine (21 mL) was cooled rapidly to form crystals. 3-Butyn-1-ol (14.0 g, 0.200 mol) was then added dropwise with cooling. The reaction mixture was warmed to room temperature and stirred overnight, then cooled to 0 °C and diluted with water (30 mL). The

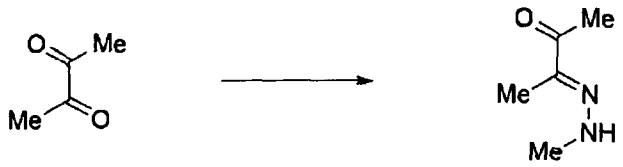
resulting suspension was then poured into water (45 mL) and extracted with ether (4 × 50 mL). The combined organics were washed with sulphuric acid (2 M; 4 × 100 mL), saturated sodium hydrogen carbonate (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a colourless oil (32.4 g, 72%); ν_{max} (film)/cm^{-1} 3292 (alkyne C-H), 2125 (C≡C), 1598 (C=C), 1496 (C=C), 1464 (C=C), 1360 (S=O); δ_H (300 MHz; $CDCl_3$) 7.81 (2 H, d, J = 8.3 Hz, ArH), 7.36 (2 H, d, J = 8.3 Hz, ArH), 4.11 (2 H, t, J = 7.0 Hz, OCH_2), 2.56 (2 H, dt, J = 7.0, 2.6 Hz, CH_2), 2.46 (3 H, s, Me), 1.97 (1 H, t, J = 2.6 Hz, C≡CH); δ_C (75 MHz; $CDCl_3$) 145.5 (C), 133.2 (C), 130.3 (CH), 128.4 (CH), 78.8 (C≡<u>C</u>H), 71.2 (<u>C</u>≡CH), 67.8 (CH_2), 22.1 (Me), 19.8 (CH_2).

4-Iodobut-1-yne[96] **266**

265 **266**

To a stirred solution of toluene-4-sulfonic acid but-3-ynyl ester **265** (15.0 g, 66.9 mmol) in acetone (50 mL) was added sodium iodide (10.0 g, 66.7 mmol). The reaction mixture was stirred for 3 d and the solvent boiled off at atmospheric pressure. The crude product was distilled at room temperature *in vacuo* to afford the title compound as a colourless oil (5.58 g, 46%); ν_{max} (film)/cm^{-1} 3293 (alkyne C-H), 2119 (C≡C), 1175 (C-I); δ_H (300 MHz; $CDCl_3$) 3.24 (2 H, t, J = 7.4 Hz, CH_2I), 2.80 (2 H, dt, J = 7.4, 2.5 Hz, CH_2), 2.17 (1 H, t, J = 2.5 Hz, C≡CH); δ_C (75 MHz; $CDCl_3$) 81.9 (C≡<u>C</u>H), 69.4 (<u>C</u>≡CH), 22.8 (CH_2), 0.0 (CH_2I).

3-(Methylhydrazono)-butan-2-one[97] 268



242 **268**

Following general procedure 2, the title compound was obtained from 2,3-butanedione **242** (1.72 g, 20.0 mmol) and methylhydrazine (1.01 g, 22.0 mmol) as a colourless oil (1.37 g, 60%); ν_{max} ($CHCl_3$)/cm^{-1} 3298 (NH), 1726 (C=O), 1651 (C=N); δ_H (300 MHz; $CDCl_3$) 5.75 (1 H, br s, NH), 3.24 (3 H, s, NMe), 2.36 (3 H, s, Me), 1.79 (3 H, s, Me); δ_C (75 MHz; $CDCl_3$) 197.6 (C), 140.3 (C), 38.4 (NMe), 24.1 (Me), 7.42 (Me).

Hydrazine carboxylic acid benzyl ester[98]

To a stirred solution of hydrazine monohydrate (5.01 g, 0.100 mol) in CH_2Cl_2 (100 mL) at 0 °C was added triethylamine (12.1 g, 0.120 mol) and benzyl chloroformate (18.8 g, 0.110 mol). Stirring was continued at 0 °C for 4.5 h, and the reaction mixture was then diluted with water (75 mL), separated, and the aqueous layer extracted with dichloromethane (2 × 50 mL). The combined organics were washed with brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate followed by methanol to afford the title compound as a colourless solid (3.55 g, 21%); (Found: MH^+, 167.0840. $C_8H_{10}N_2O_2$ + H requires 167.0820); ν_{max} (KBr)/cm^{-1} 3331 (NH_2), 3212 (NH_2), 1690 (C=O), 1650 (C=C), 1520 (C=C), 1465 (C=C); δ_H (300 MHz; $CDCl_3$) 7.43 - 7.29 (5 H, m, ArH), 6.02 (1 H, br s, NH), 5.15 (2 H, s, CH_2), 3.75 (2 H, br s, NH_2); δ_C (75

MHz; $CDCl_3$) 159.1 (C), 136.4 (C), 129.0 (CH), 128.8 (CH), 128.6 (CH), 67.7 (CH_2); *m/z* (CI) 423 (8%), 257 (85), 213 (30), 167 (15), 123 (17), 119 (10), 91 (100).

N'-(1-Methyl-2-oxo-propylidene)-hydrazinecarboxylic acid benzyl ester 269

269

Following general procedure 2, the *title compound* was obtained from 2,3-butanedione **242** (0.430 g, 5.00 mmol) and hydrazine carboxylic acid benzyl ester (0.914 g, 5.50 mmol) as a colourless solid (1.01 g, 86%), mp 131-133 °C (from dichloromethane-hexane); (Found: MH^+, 235.1078. $C_{12}H_{14}N_2O_3$ + H requires 235.1082); ν_{max} (KBr)/cm^{-1} 3454 (NH), 1711 (C=O), 1683 (C=O), 1605 (C=C), 1485 (C=C); δ_H (300 MHz; $CDCl_3$) 7.97 (1 H, br s, NH), 7.45 - 7.36 (5 H, m, ArH), 5.30 (2 H, s, CH_2), 2.47 (3 H, s, Me), 1.92 (3 H, s, Me); δ_C (75 MHz; $CDCl_3$) 198.1 (C), 135.6 (C), 129.1 (CH), 128.9 (CH), 68.7 (CH_2), 24.9 (Me), 8.7 (Me); *m/z* (CI) 325 (35%), 263 (5), 235 (MH^+, 55), 191 (12), 91 (100).

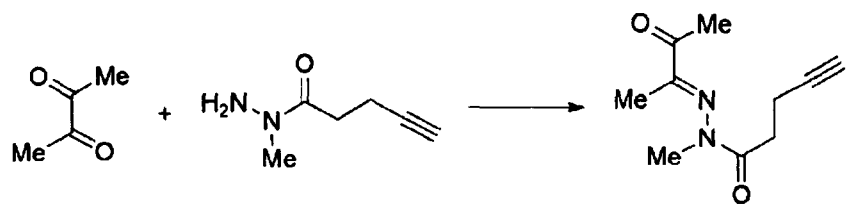
N-methylpent-4-ynehydrazide[29] 273

273

A solution of 4-pentynoic acid (5.00 g, 51.0 mmol) in freshly distilled thionyl chloride (3.71 mL, 51.0 mmol) was heated under reflux for 45 min. The reaction mixture was cooled to room temperature, diluted with dichloromethane (14 mL) and added dropwise to a solution of methylhydrazine (9.21 g, 200 mmol) in dichloromethane (50

mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and the solid filtered off. The filtrate was concentrated *in vacuo*, and the crude product purified by flash chromatography on silica gel, eluting with methanol-ethyl acetate (0:1 to 1:19) to afford the title compound as a pale yellow solid (3.30 g, 51%), mp 57-59 °C (from dichloromethane-hexane) (lit.,[29] 52-54 °C); δ_H (400 MHz; $CDCl_3$) two rotomers, 3.87 (2 H, br s, NH_2), 3.24 and 3.20 (3 H, s, NMe), 2.88 (1 H, t, J = 7.2 Hz, C$\underline{H_2}$), 2.58-2.49 (3 H, m, CH_2 + C$\underline{H_2}$), 1.99 and 1.96 (1 H, t, J = 2.8 Hz, C≡CH); δ_C (100 MHz; $CDCl_3$) two rotomers, 68.9 (C≡CH), 68.3 (C≡CH), 38.7 and 38.5 (NMe), 31.9 and 31.8 (CH_2), 15.51 and 15.5 (CH_2).

(*E*)-*N*-Methyl-*N'*-(3-oxobutan-2-ylidene)pent-4-ynehydrazide 274

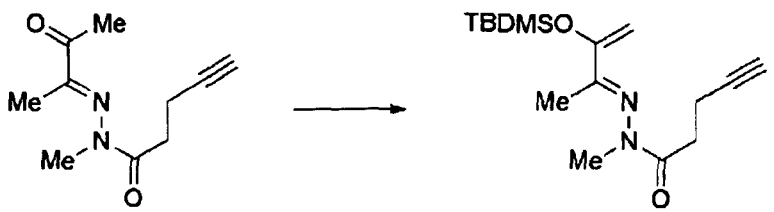


242 **273** **274**

To a solution of 2,3-butanedione **242** (0.861 g, 10.0 mmol) in ethanol (3 mL) at 0 °C was added hydrazide **273** (1.39 g, 11.0 mmol) in ethanol (7 mL) dropwise over 15 min. The reaction mixture was stirred at 0 °C for 3.5 h, then allowed to warm to room temperature and stirred for a further 18 h. The resulting solution was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:5) to afford the *title compound* as a colourless solid (1.83 g, 94%), mp 90-92 °C (from dichloromethane-hexane); ν_{max} ($CHCl_3$)/cm^{-1} 3308 (alkyne C-H), 2121 (C≡C), 1690 (C=O), 1606 (C=N); (Found: MH^+, 195.1125. $C_{10}H_{14}N_2O_2$ + H requires 195.1128); δ_H (400 MHz; $CDCl_3$) 3.45 (3 H, s, NMe), 3.0-2.96 (2 H, m, CH_2), 2.60-2.56 (2 H, m,

CH_2), 2.44 (3 H, s, Me), 2.19 (3 H, s, Me), 1.98 (1 H, t, J = 2.8 Hz, C≡CH); δ_C (100 MHz; $CDCl_3$) 198.3 (C), 174.5 (C), 83.3 (C≡CH), 68.7 (C≡CH), 35.3 (NMe), 33.3 (CH_2), 25.2 (Me), 14.3 (CH_2), 14.0 (Me); *m/z* (ESI) 217 (MNa^+, 100%), 195 (11).

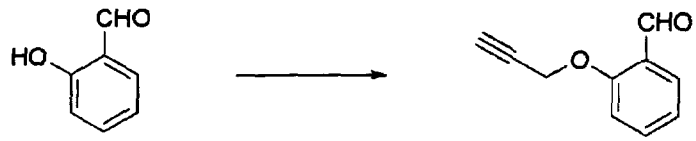
(*E*)-*N'*-(3-(*tert*-Butyldimethylsilyloxy)but-3-en-2-ylidene)-*N*-methylpent-4-ynehydrazide 275



274 **275**

Following general procedure 3, the *title compound* was obtained from α-ketohydrazide **274** (0.777 g, 4.00 mmol) as a pale orange oil (1.24 g, 100%); (Found: MH^+, 309.1979. $C_{16}H_{28}N_2O_2Si$ + H requires 309.1993); ν_{max} ($CHCl_3$)/cm^{-1} 3308 (alkyne CH), 2121 (C≡C), 1718 (C=O), 1664 (C=O), 1606 (C=C); δ_H (400 MHz; $CDCl_3$) 5.10 (1 H, d, J = 1.6 Hz, C=CH), 4.62 (1 H, d, J = 1.6 Hz, C=CH), 3.15 (3 H, s, NMe), 2.61-2.58 (2 H, m, CH_2), 2.54-2.51 (2 H, m, CH_2), 2.05 (3 H, s, Me), 1.95 (1 H, t, J = 1.5 Hz, C≡CH), 0.98 (9 H, s, CMe_3), 0.11 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 172.3 (C), 167.2 (C), 154.1 (C), 97.8 (CH_2), 83.6 (C≡CH), 68.4 (C≡CH), 35.6 (NMe), 32.7 (CH_2), 25.4 (CMe_3), 18.2 (CMe_3), 16.0 (Me), 14.0 (CH_2), -4.7 ($SiMe_2$); *m/z* (ESI) 331 (MNa^+, 100%), 309 (MH^+, 87).

2-(Prop-2-ynyloxy)benzaldehyde[59] 322



320 **322**

Following general procedure 6, the title compound was obtained from salicaldehyde **320** (0.305 g, 2.50 mmol), potassium carbonate (0.518 g, 3.75 mmol) and propargyl chloride (0.90 mL, 12.5 mmol) as a colourless oil (0.400 g, 100%); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C-H), 2127 (C≡C), 1690 (C=O), 1601 (C=C), 1483 (C=C), 1460 (C=C), 1023 (C-O); δ_H (400 MHz; $CDCl_3$) 10.47 (1 H, s, CHO), 7.85 (1 H, d, J = 7.6 Hz, ArH), 7.55 (1 H, t, J = 7.6 Hz, ArH), 7.12 - 7.05 (2 H, m, ArH), 4.82 (2 H, d, J = 2.4 Hz, CH_2), 2.58 (1 H, t, J = 2.4 Hz, C≡CH); δ_C (100 MHz; $CDCl_3$) 189.5 (CHO), 159.8 (C), 135.7 (CH), 128.5 (CH), 125.5 (C), 121.7 (CH), 113.2 (CH), 77.7 (C≡CH), 76.5 (C≡CH), 56.4 (CH_2);

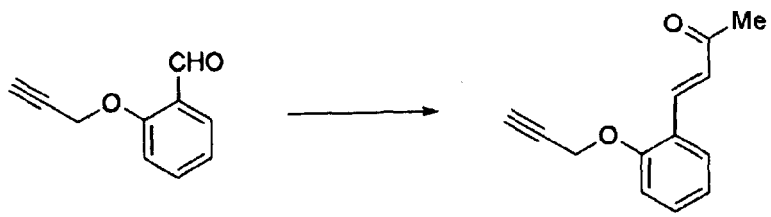
3-Methyl-2-(prop-2-ynyloxy)benzaldehyde 323

321 **323**

Following general procedure 6, the title compound was obtained from 3-methylsalicaldehyde **321** (0.340 g, 2.50 mmol), potassium carbonate (0.518 g, 3.75 mmol) and propargyl chloride (0.90 mL, 12.5 mmol) as a colourless oil (0.375 g, 86%); (Found: MH^+, 175.0758. $C_{11}H_{10}O_2$ + H requires 175.0754); ν_{max} ($CHCl_3$)/cm^{-1} 3306 (alkyne C-H), 2126 (C≡C), 1693 (C=O), 1588 (C=C), 1469 (C=C), 1249 (C-O), 1086 (C-O); δ_H (400 MHz; $CDCl_3$) 10.42 (1 H, s, CHO), 7.71 (1 H, d, J = 7.6 Hz, H-6), 7.45 (1 H, d, J = 7.6 Hz, H-4), 7.17 (1 H, t, J = 7.6 Hz, H-5), 4.68 (2 H, d, J = 2.0

Hz, CH_2), 2.54 (1 H, t, J = 2.0 Hz, C≡CH), 2.36 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 190.6 (CH), 158.9 (C), 137.5 (CH), 132.4 (C), 130.2 (C), 126.5 (CH), 125.0 (CH), 77.9 (C), 76.8 (CH), 62.1 (CH_2), 15.9 (Me); *m/z* (ESI) 197 (MNa^+, 100%), 175 (MH^+, 37), 147 (66).

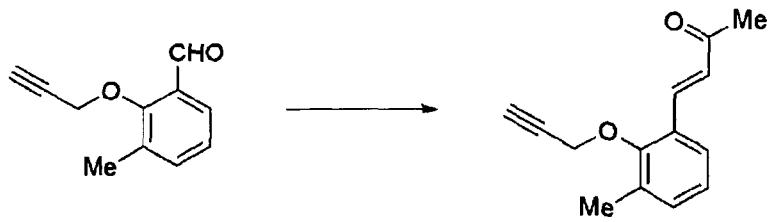
(*E*)-4-(2-(Prop-2-ynyloxy)phenyl)but-3-en-2-one[59] 326



322 **326**

Following general procedure 7, the title compound was obtained from 2-(prop-2-ynyloxy)benzaldehyde **322** (0.288 g, 1.80 mmol), sodium hydride (0.108 g, 2.70 mmol) and dimethyl 2-oxopropylphosphonate **324** (0.448 g, 2.70 mmol) as a colourless oil (0.329 g, 91%); δ_H (400 MHz; $CDCl_3$) 7.88 (1 H, d, J = 16.4 Hz, C=CH), 7.56 (1 H, d, J = 7.6 Hz, H-10), 7.37 (1 H, t, J = 7.6 Hz, H-9), 7.05 (1 H, d, J = 7.6 Hz, H-7), 7.02 (1 H, t, J = 7.6 Hz, H-8), 6.73 (1 H, d, J = 16.4 Hz, C=CH), 4.78 (2 H, d, J = 1.2 Hz, CH_2), 2.55 (1 H, t, J = 1.2 Hz, C≡CH), 2.38 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 199.0 (C), 156.1 (C), 138.4 (CH), 131.6 (CH), 128.3 (CH), 128.1 (CH), 124.0 (C), 121.8 (CH), 112.8 (CH), 78.1 (C), 76.1 (CH), 56.2 (CH_2), 27.2 (Me).

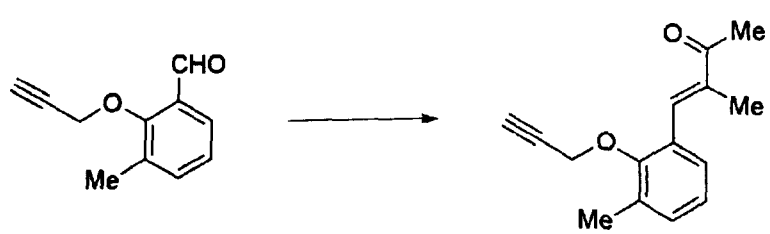
(*E*)-4-(3-Methyl-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one 327



323 **327**

Following general procedure 7, the *title compound* was obtained from 3-methyl-2-(prop-2-ynyloxy)benzaldehyde **323** (0.314 g, 1.80 mmol), sodium hydride (0.108 g, 2.70 mmol) and dimethyl 2-oxopropylphosphonate **324** (0.448 g, 2.70 mmol) as a colourless oil (0.340 g, 88%); (Found: MH^+, 215.1077. $C_{14}H_{14}O_2$ + H requires 215.1066); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C-H), 2127 (C≡C), 1669 (C=O), 1644 (C=C), 1623 (C=C), 1607 (C=C), 1462 (C=C), 1259 (C-O), 1090 (C-O); δ_H (400 MHz; $CDCl_3$) 7.94 (1 H, d, *J* = 16.4 Hz, C=CH), 7.44 (1 H, d, *J* = 7.6 Hz, H-10), 7.24 (1 H, d, *J* = 7.6 Hz, H-8), 7.08 (1 H, t, *J* = 7.6 Hz, H-9), 6.69 (1 H, d, *J* = 16.4 Hz, C=CH), 4.55 (2 H, d, *J* = 1.2 Hz, CH_2), 2.55 (1 H, t, *J* = 1.2 Hz, C≡CH), 2.41 (3 H, s, Me), 2.34 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 198.9 (C), 156.0 (C), 139.0 (CH), 133.6 (CH), 132.1 (C), 128.5 (CH), 128.4 (C), 125.2 (CH), 125.0 (CH), 78.6 (C), 76.1 (CH), 61.4 (CH_2), 27.0 (Me), 16.4 (Me); *m/z* (ESI) 237 (MNa^+, 61%), 215 (MH^+, 100).

(*E*)-3-Methyl-4-(3-methyl-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one 328

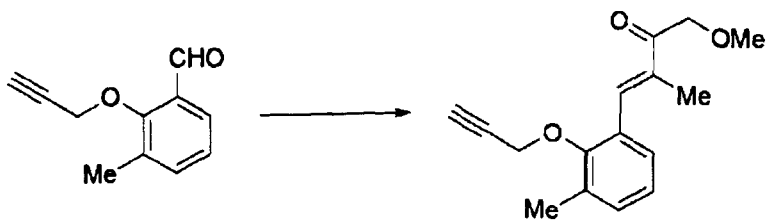


323 **328**

Following general procedure 7, the *title compound* was obtained from 3-methyl-2-(prop-2-ynyloxy)benzaldehyde **323** (0.401 g, 2.30 mmol), potassium *tert*-butoxide

(0.387 g, 3.45 mmol) and diethyl 1-methyl-2-oxopropylphosphonate **319** (0.718 g, 3.45 mmol) as a colourless oil (0.420 g, 82%); (Found: MH^+, 229.1227. $C_{15}H_{16}O_2$ + H requires 229.1223); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C-H), 2128 (C≡C), 1665 (C=O), 1623 (C=C), 1586 (C=C), 1461 (C=C), 1263 (C-O), 1089 (C-O); δ_H (400 MHz; $CDCl_3$) 7.78 (1 H, s, C=CH), 7.23-7.20 (2 H, m, ArH), 7.10 (1 H, t, J = 7.6 Hz, H-9), 4.50 (2 H, d, J = 1.3 Hz, CH_2), 2.52 (1 H, t, J = 1.3 Hz, C≡CH), 2.51 (3 H, s, Me), 2.37 (3 H, s, Me), 2.01 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 200.5 (C), 155.2 (C), 138.6 (C), 136.0 (CH), 131.8 (CH), 131.7 (C), 129.5 (C), 128.2 (CH), 124.3 (CH), 78.9 (C), 75.6 (CH), 61.0 (CH_2), 26.0 (Me), 16.4 (Me), 13.0 (Me); *m/z* (ESI) 251 (MNa^+, 75%), 229 (MH^+, 100).

(*E*)-1-Methoxy-3-methyl-4-(3-methyl-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one 329

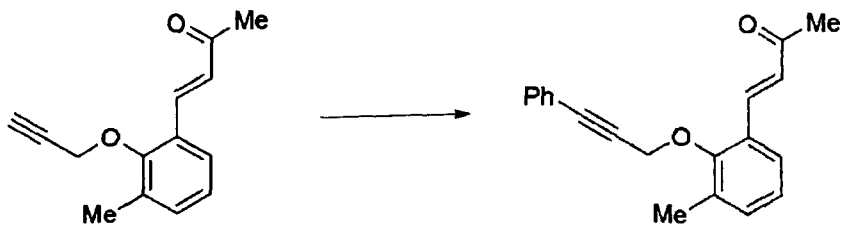


323 **329**

To a solution of potassium *tert*-butoxide (0.421 g, 3.75 mmol) in toluene (4 mL) was added diethyl 4-methoxy-3-oxobutan-2-ylphosphonate **325** (0.893 g, 3.75 mmol) in toluene (3 mL) dropwise over 15 min. The reaction mixture was stirred for 30 min, followed by dropwise addition of 3-methyl-2-(prop-2-ynyloxy)benzaldehyde **323** (0.436 g, 2.50 mmol) in toluene (3 mL) over 15 min. The resulting mixture was stirred at room temperature for 16 h and partitioned between saturated ammonium chloride (45 mL) and ethyl acetate (3 × 45 mL). The combined organic extracts were washed with water (45 mL) and saturated brine (45 mL), dried over $MgSO_4$ and concentrated

in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9), to afford the title compound as a colourless oil (0.487 g, 75%); (Found: MH^+, 259.1336. $C_{16}H_{18}O_3$ + H requires 259.1329); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C-H), 2127 (C≡C), 1683 (C=O), 1627 (C=C), 1586 (C=C), 1461 (C=C), 1261 (C-O), 1090 (C-O), 1056 (C-O); δ_H (400 MHz; $CDCl_3$) 7.70 (1 H, s, C=CH), 7.23-7.20 (2 H, m, ArH), 7.09 (1 H, t, J = 7.6 Hz, H-9), 4.61 (2 H, s, CH_2), 4.49 (2 H, d, J = 1.2 Hz, CH_2), 3.49 (3 H, s, OMe), 2.53 (1 H, t, J = 1.2 Hz, C≡CH), 2.35 (3 H, s, Me), 2.03 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 197.9 (C), 155.2 (C), 136.1 (C), 135.2 (CH), 132.1 (CH), 131.8 (C), 129.1 (C), 128.1 (CH), 124.4 (CH), 78.9 (C), 75.7 (CH), 74.8 (CH_2), 61.1 (CH_2), 59.4 (Me), 16.4 (Me), 13.1 (Me); *m/z* (ESI) 281 (MNa^+, 100%), 259 (MH^+, 42), 241 (72).

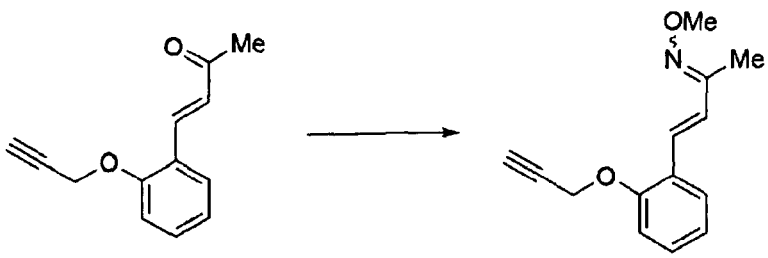
(*E*)-4-(2-(3-Phenylprop-2-ynyloxy)-3-methylphenyl)but-3-en-2-one 339



Following general procedure 8, the *title compound* was obtained from iodobenzene (0.67 mL, 6.00 mmol) and alkyne **327** (0.857 g, 4.00 mmol as a colourless oil (0.768 g, 66%); (Found: MH^+, 291.1382. $C_{20}H_{18}O_2$ + H requires 291.1380); ν_{max} ($CHCl_3$)/cm^{-1} 2233 (C≡C), 1669 (C=C), 1644 (C=C), 1622 (C=C), 1606 (C=C), 1588 (C=C), 1491 (C=C), 1461 (C=C), 1443 (C=C), 1260 (C-O), 1090 (C-O); δ_H (400 MHz; $CDCl_3$) 8.05 (1 H, d, J = 16.5 Hz, C=CH), 7.49 (1 H, d, J = 7.6 Hz, H-10), 7.40-7.38 (2 H, m, ArH), 7.35-7.32 (3 H, m, ArH), 7.28 (1 H, d, J = 7.2 Hz, H-8), 7.12 (1 H, t, J = 7.6 Hz, H-9), 6.72 (1 H, d, J = 16.5 Hz, C=CH), 4.81 (2 H, s, CH_2), 2.41 (3 H, s, Me), 2.34 (3

H, s, Me); δ_C (100 MHz; $CDCl_3$) 199.0 (C), 156.0 (C), 139.2 (CH), 133.6 (CH), 132.3 (C), 131.6 (CH), 128.8 (CH), 128.7 (C), 128.4 (CH), 128.1 (CH), 125.1 (CH), 125.0 (CH), 122.1 (C), 87.9 (C), 84.0 (C), 62.3 (CH_2), 26.9 (Me), 16.5 (Me); *m/z* (ESI) 313 (MNa^+, 51%), 291 (MH^+, 100).

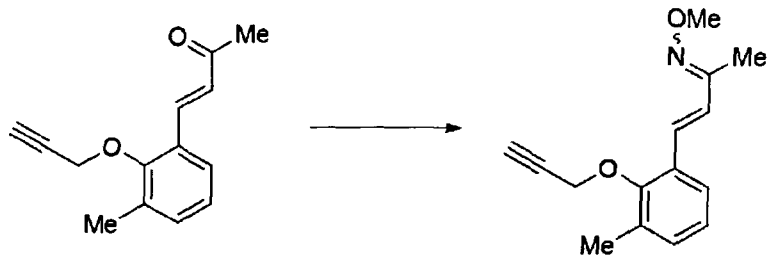
(3*E*)-4-(2-(Prop-2-ynyloxy)phenyl)but-3-en-2-one *O*-methyloxime 330



326 **330**

Following general procedure 9, the *title compound* was obtained from ketone **326** (0.280 g, 1.40 mmol), methoxylamine hydrochloride (0.146 g, 1.75 mmol) and sodium acetate (0.200 g, 1.47 mmol) as a colourless oil (0.314 g, 98%); (Found: MH^+, 230.1192. $C_{14}H_{15}NO_2$ + H requires 230.1181); ν_{max} ($CHCl_3$)/cm^{-1} 3308 (alkyne C-H), 2125 (C≡C), 1600 (C=C), 1487 (C=C), 1457 (C=C), 1240 (C-O), 1055 (C-O); δ_H (400 MHz; $CDCl_3$) 7.57 (1 H, d, J = 7.6 Hz, H-10), 7.35 - 7.24 (2 H, m, ArH + C=CH), 7.04 - 6.86 (2 H, m, ArH), 6.85 (1 H, d, J = 16.4 Hz, C=CH), 4.77 (2 H, d, J = 1.2 Hz, CH_2), 3.96 (3 H, s, OMe), 2.54 (1 H, t, J = 1.2 Hz, C≡CH), 2.10 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.3 (C), 154.9 (C), 145.8 (C), 129.2 (CH), 127.3 (CH), 126.6 (CH), 126.4 (CH), 121.8 (CH), 112.8 (CH), 78.5 (C), 75.8 (CH), 61.8 (Me), 56.3 (CH_2), 10.2 (Me); *m/z* (ESI) 252 (MNa^+, 11%), 230 (MH^+, 100).

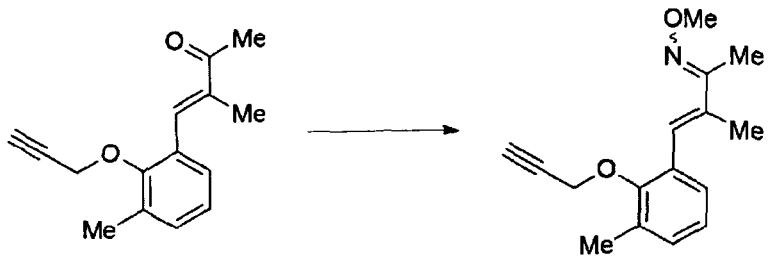
(3*E*)-4-(3-Methyl-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one *O*-methyloxime 331



327 **331**

Following general procedure 9, the *title compound* was obtained from ketone **327** (0.300 g, 1.40 mmol), methoxylamine hydrochloride (0.146 g, 1.75 mmol) and sodium acetate (0.200 g, 1.47 mmol) as a colourless oil (0.333 g, 98%); (Found: MH^+, 244.1346. $C_{15}H_{17}NO_2$ + H requires 244.1332); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C-H), 2127 (C≡C), 1619 (C=C), 1586 (C=C), 1462 (C=C), 1240 (C-O), 1056 (C-O); δ_H (400 MHz; $CDCl_3$) 7.43 (1 H, d, J = 6.8 Hz, H-10), 7.29 (1 H, d, J = 16.8 Hz, C=CH), 7.13 (1 H, d, J = 7.2 Hz, H-8), 7.05 (1 H, t, J = 7.2 Hz, H-9), 6.81 (1 H, d, J = 16.8 Hz, C=CH), 4.51 (2 H, d, J = 1.2 Hz, CH_2), 3.96 (3 H, s, OMe), 2.54 (1 H, t, J = 1.2 Hz, C≡CH), 2.34 (3 H, s, Me), 2.12 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.1 (C), 154.8 (C), 131.9 (C), 131.2 (CH), 130.2 (C), 127.9 (CH), 126.9 (CH), 124.9 (CH), 124.0 (CH), 79.0 (C), 75.6 (CH), 61.9 (Me), 61.1 (CH_2), 16.4 (Me), 10.2 (Me); *m/z* (ESI) 266 (MNa^+, 22%), 244 (MH^+, 100).

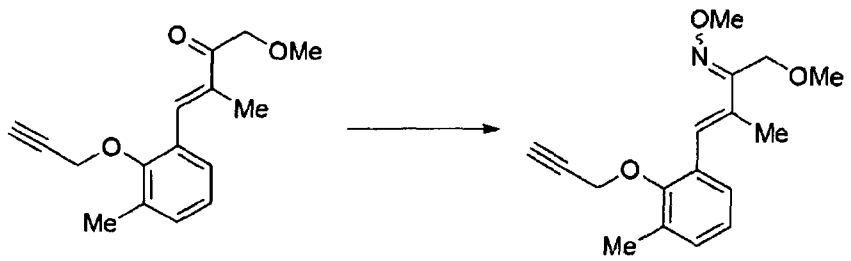
(3*E*)-3-Methyl-4-(3-methyl-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one *O*-methyl oxime 332



328 **332**

Following general procedure 9, the *title compound* was obtained from ketone **328** (0.297 g, 1.30 mmol), methoxylamine hydrochloride (0.136 g, 1.63 mmol) and sodium acetate trihydrate (0.186 g, 1.37 mmol) as a colourless oil (0.242 g, 72%); (Found: MH^+, 258.1497. $C_{16}H_{19}NO_2$ + H requires 258.1489); ν_{max} ($CHCl_3$)/cm^{-1} 3308 (alkyne C-H), 2128 (C≡C), 1586 (C=C), 1461 (C=C), 1253 (C-O), 1055 (C-O); δ_H (400 MHz; $CDCl_3$) 7.14 - 7.13 (2 H, m, ArH), 7.06 (1 H, d, J = 7.6 Hz, H-8), 7.01 (1 H, s, C=CH), 4.47 (2 H, d, J = 1.2 Hz, CH_2), 3.97 (3 H, s, OMe), 2.48 (1 H, t, J = 1.2 Hz, C≡CH), 2.36 (3 H, s, Me), 2.15 (3 H, s, Me), 2.06 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.9 (C), 155.0 (C), 135.7 (C), 131.5 (C), 130.7 (C), 130.3 (CH), 128.6 (CH), 126.5 (CH), 124.0 (CH), 79.3 (C), 75.0 (CH), 61.8 (Me), 60.5 (CH_2), 16.5 (Me), 14.4 (Me), 10.8 (Me); *m/z* (ESI) 280 (MNa^+, 32%), 258 (MH^+, 100).

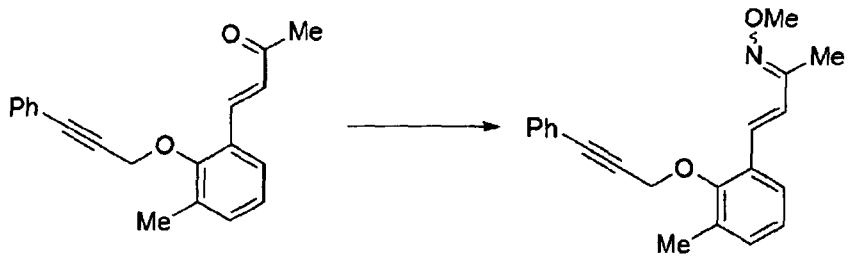
(3*E*)-1-Methoxy-3-methyl-4-(3-methyl-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one *O*-methyloxime 333



329 **333**

Following general procedure 9, the *title compound* was obtained from ketone **329** (0.387 g, 1.50 mmol), methoxylamine hydrochloride (0.157 g, 1.88 mmol) and sodium acetate trihydrate (0.214 g, 1.58 mmol) as a colourless oil (0.410 g, 95%); (Found: MH^+, 288.1603. $C_{17}H_{21}NO_3$ + H requires 288.1594); ν_{max} ($CHCl_3$)/cm^{-1} 3308 (alkyne C-H), 2127 (C≡C), 1596 (C=C), 1461 (C=C), 1254 (C-O), 1051 (C-O); δ_H (400 MHz; $CDCl_3$) 7.18-7.13 (2 H, m, ArH), 7.06 (1 H, d, J = 7.4 Hz, H-8), 4.52 (2 H, d, J = 1.2 Hz, CH_2), 4.51 (2 H, s, CH_2), 3.99 (3 H, s, OMe), 3.43 (3 H, s, OMe), 2.50 (1 H, t, J = 1.2 Hz, C≡CH), 2.49 (3 H, s, Me), 2.03 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.7 (C), 154.8 (C), 133.3 (C), 131.6 (C), 130.6 (C), 130.5 (CH), 128.6 (CH), 127.8 (CH), 123.9 (CH), 79.4 (C), 75.0 (CH), 62.3 (CH_2), 62.0 (Me), 60.4 (CH_2), 58.6 (Me), 16.6 (Me), 14.6 (Me); *m/z* (ESI) 310 (MNa^+, 67%), 288 (MH^+, 100).

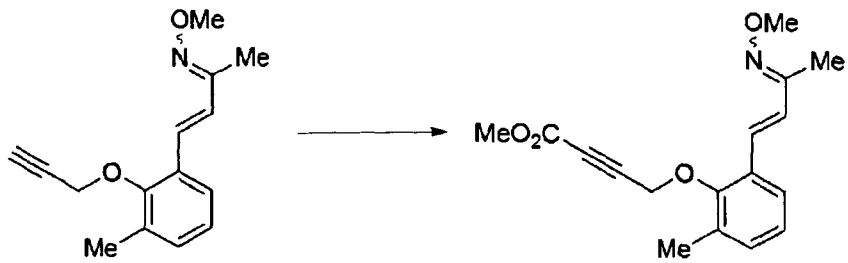
(3*E*)-4-(2-(3-Phenylprop-2-ynyloxy)-3-methylphenyl)but-3-en-2-one *O*-methyl oxime 340



339 **340**

Following general procedure 9, the title compound was obtained from ketone **339** (0.667 g, 2.30 mmol), methoxylamine hydrochloride (0.240 g, 2.88 mmol) and sodium acetate trihydrate (0.329 g, 2.42 mmol) as a colourless oil (0.690 g, 94%); (Found: MH^+, 320.1661. $C_{21}H_{21}NO_2$ + H requires 320.1645); ν_{max} ($CHCl_3$)/cm^{-1} 2235 (C≡C), 1599 (C=C), 1491 (C=C), 1462 (C=C), 1443 (C=C), 1244 (C-O), 1056 (C-O); δ_H (400 MHz; $CDCl_3$) 7.49-7.31 (7 H, m, 6 × ArH + C=CH), 7.17 (1 H, d, J = 7.4 Hz, H-8), 7.08 (1 H, t, J = 7.4 Hz, H-9), 6.86 (1 H, d, J = 16.6 Hz, C=CH), 4.77 (2 H, s, CH_2), 3.97 (3 H, s, OMe), 2.41 (3 H, s, Me), 2.08 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.2 (C), 155.0 (C), 131.9 (CH), 131.8 (C), 131.2 (CH), 130.3 (C), 128.6 (CH), 128.3 (CH), 128.1 (CH), 126.7 (CH), 124.8 (CH), 124.0 (CH), 122.3 (C), 87.4 (C≡CPh), 84.3 (C≡CPh), 62.0 (CH_2), 61.9 (OMe), 16.5 (Me), 10.2 (Me); *m/z* (ESI) 342 (MNa^+, 42%), 320 (MH^+, 100), 288 (30).

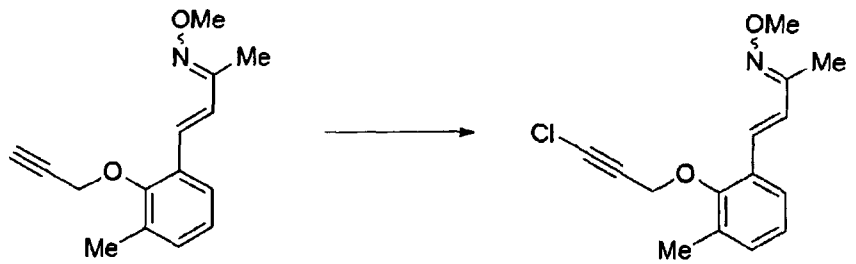
(3*E*)-4-(2-(3-Methoxycarbonylprop-2-ynyloxy)-3-methylphenyl)but-3-en-2-one *O*-methyl oxime 341



331 **341**

Following general procedure 10, the *title compound* was obtained from *O*-methyl oxime **331** (0.973 g, 4.00 mmol) and methyl chloroformate (0.46 mL, 6.00 mmol) as a colourless oil (0.495 g, 41%); (Found: MH^+, 302.1388. $C_{17}H_{19}NO_4$ + H requires 302.1387); ν_{max} ($CHCl_3$)/cm^{-1} 2245 (C≡C), 1717 (C=O), 1585 (C=C), 1462 (C=C), 1436 (C=C), 1266 (C-O), 1056 (C-O); δ_H (400 MHz; $CDCl_3$) 7.43 (1 H, d, J = 7.6 Hz, H-10), 7.23 (1 H, d, J = 16.5 Hz, C=CH), 7.14 (1 H, d, J = 7.6 Hz, H-8), 7.07 (1 H, t, J = 7.6 Hz, H-9), 6.82 (1 H, d, J = 16.5 Hz, C=CH), 4.65 (2 H, s, CH_2), 3.86 (3 H, s, OMe), 3.77 (3 H, s, OMe), 2.34 (3 H, s, Me), 2.11 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.1 (C), 154.5 (C), 153.3 (C), 131.6 (C), 131.3 (CH), 130.2 (C), 127.5 (CH), 127.4 (CH), 125.2 (CH), 124.3 (CH), 82.6 (C), 78.6 (C), 61.9 (Me), 60.6 (CH_2), 52.8 (Me), 16.4 (Me), 10.2 (Me); *m/z* (ESI) 324 (MNa^+, 100%), 302 (MH^+, 17).

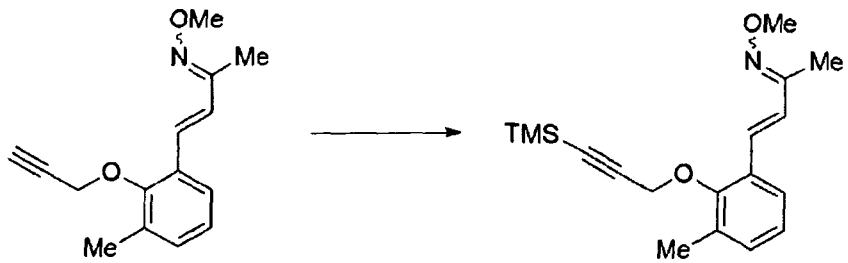
(3*E*)-4-(2-(3-Chloroprop-2-ynyloxy)-3-methylphenyl)but-3-en-2-one *O*-methyl oxime 342



331 **342**

Following general procedure 10, the *title compound* was obtained from *O*-methyl oxime **331** (0.973 g, 4.00 mmol) and *N*-chlorosuccinimide (0.801 g, 6.00 mmol) as a colourless oil (0.546 g, 49%); (Found: MH^+, 278.0947. $C_{15}H_{16}{}^{35}ClNO_2$ + H requires 278.0942); ν_{max} ($CHCl_3$)/cm^{-1} 2245 (C≡C), 1627 (C=C), 1586 (C=C), 1463 (C=C), 1056 (C-O); δ_H (400 MHz; $CDCl_3$) 7.44 (1 H, d, J = 7.6 Hz, H-8), 7.28 (1 H, d, J = 16.6 Hz, C=CH), 7.13 (1 H, d, J = 7.6 Hz, H-10), 7.06 (1 H, t, J = 7.6 Hz, H-9), 6.82 (1 H, d, J = 16.6 Hz, C=CH), 4.52 (2 H, s, CH_2), 3.97 (3 H, s, OMe), 2.33 (3 H, s, Me), 2.13 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.1 (C), 154.7 (C), 131.7 (C), 131.3 (CH), 130.3 (C), 127.8 (CH), 126.8 (CH), 125.0 (CH), 124.0 (CH), 66.0 (C), 64.9 (C), 61.9 (Me), 61.5 (CH_2), 16.3 (Me), 10.2 (Me); *m/z* (ESI) *m/z* (ESI) 280/278 (MH^+, 36/100%), 246 (30).

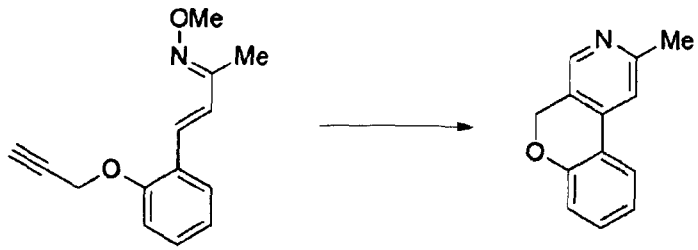
(3*E*)-4-(2-(3-Trimethylsilylprop-2-ynyloxy)-3-methylphenyl)but-3-en-2-one *O*-methyl oxime 343



331 **343**

Following general procedure 10, the *title compound* was obtained from *O*-methyl oxime **331** (0.973 g, 4.00 mmol) and chlorotrimethylsilane (0.77 mL, 6.00 mmol) as a colourless oil (0.664 g, 53%); (Found: MH^+, 316.1724. $C_{18}H_{25}NO_2Si$ + H requires 316.1727); ν_{max} ($CHCl_3$)/cm^{-1} 2181 (C≡C), 1625 (C=C), 1586 (C=C), 1462 (C=C), 1056 (C-O), 848 (C-Si); δ_H (400 MHz; $CDCl_3$) 7.44 (1 H, d, J = 7.6 Hz, H-10), 7.30 (1 H, d, J = 16.5 Hz, C=CH), 7.13 (1 H, d, J = 7.6 Hz, H-8), 7.05 (1 H, t, J = 7.6 Hz, H-9), 6.82 (1 H, d, J = 16.5 Hz, C=CH), 4.53 (2 H, s, CH_2), 3.98 (3 H, s, OMe), 2.35 (3 H, s, Me), 2.14 (3 H, s, Me), 0.18 (9 H, s, $SiMe_3$); δ_C (100 MHz; $CDCl_3$) 156.5 (C), 155.2 (C), 132.1 (C), 131.5 (CH), 130.5 (C), 128.4 (CH), 127.0 (CH), 125.1 (CH), 124.2 (CH), 100.8 (C), 93.0 (C), 62.2 (CH_2), 61.9 (OMe), 16.8 (Me), 10.6 (Me), 0.0 ($SiMe_3$); *m/z* (ESI) 338 (MNa^+, 18%), 316 (MH^+, 100).

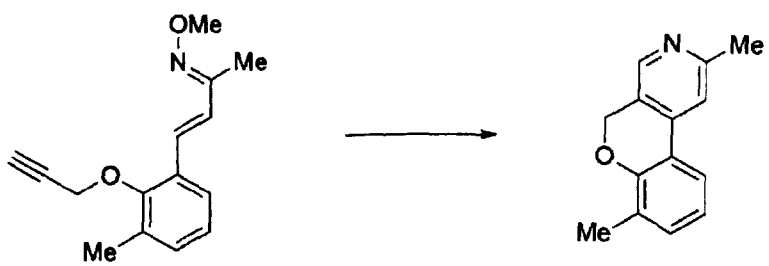
2-Methyl-5*H*-chromeno[3,4-*c*]pyridine[59] 334



330 **334**

Following general procedure 11, the title compound was obtained from *O*-methyl oxime **330** (0.115 g, 0.50 mmol) after 16 h at 180 °C as a yellow oil (0.030 g, 30%); ν_{max} ($CHCl_3$)/cm^{-1} 1610 (C=C), 1588 (C=C), 1553 (C=C), 1499 (C=C), 1485 (C=C), 1457 (C=C); δ_H (400 MHz; $CDCl_3$) 8.30 (1 H, s, H-4), 7.73 (1 H, d, J = 8.0 Hz, H-10), 7.41 (1 H, s, H-1), 7.33 (1 H, t, J = 8.0 Hz, H-9), 7.08 (1 H, t, J = 8.0 Hz, H-8), 7.01 (1 H, d, J = 8.0 Hz, H-7), 5.13 (2 H, s, CH_2), 2.61 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 158.7 (C), 155.8 (C), 145.0 (CH), 137.9 (C), 131.6 (CH), 123.9 (CH), 123.2 (C), 122.3 (CH), 120.6 (C), 117.8 (CH), 115.4 (CH), 65.8 (CH_2), 24.5 (Me).

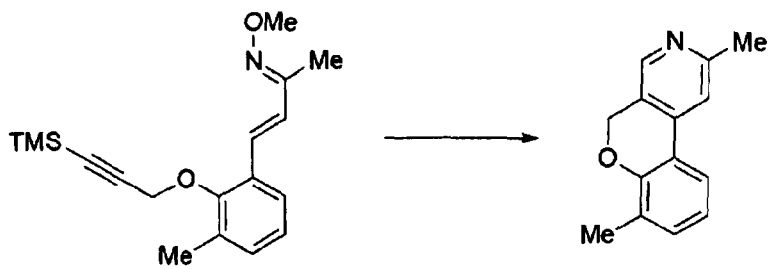
2,7-Dimethyl-5*H*-chromeno[3,4-*c*]pyridine 335



331 **335**

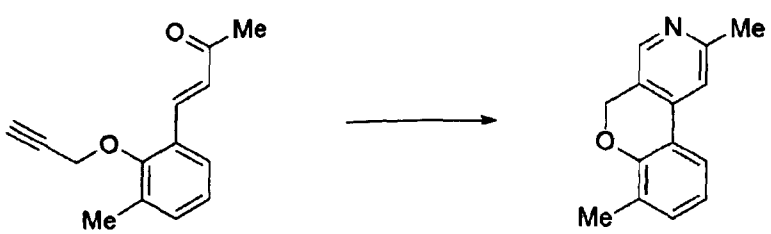
(a) Following general procedure 11, the *title compound* was obtained from *O*-methyl oxime **331** (0.122 g, 0.50 mmol) after 16 h at 180 °C as a colourless solid (0.039 g, 37%), mp 107-109 °C (from ethyl acetate-hexane); (Found: MH^+, 212.1079. $C_{14}H_{13}NO$ + H requires 212.1070); ν_{max} ($CHCl_3$)/cm^{-1} 1610 (C=C), 1599 (C=C), 1561 (C=C), 1465 (C=C), 1021 (C-O); δ_H (400 MHz; $CDCl_3$) 8.30 (1 H, s, H-4), 7.57 (1 H,

d, J = 7.7 Hz, H-10), 7.38 (1 H, s, H-1), 7.21 (1 H, d, J = 7.4 Hz, H-8), 6.97 (1 H, dd, J = 7.4 and 7.7 Hz, H-9), 5.13 (2 H, s, CH_2), 2.60 (3 H, s, Me), 2.27 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 158.6 (C), 153.9 (C), 144.9 (CH), 138.3 (C), 132.8 (CH), 127.2 (C), 123.2 (C), 121.6 (CH), 121.5 (CH), 120.1 (C), 115.5 (CH), 65.8 (CH_2), 24.6 (Me), 15.9 (Me); *m/z* (ESI) 212 (MH^+, 100%).



343 **335**

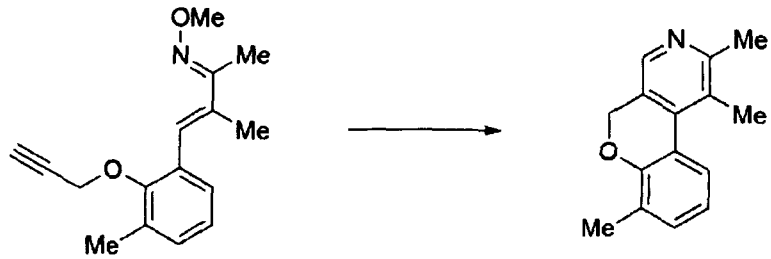
(b) Following general procedure 11, the title compound was obtained from *O*-methyl oxime **343** (0.158 g, 0.50 mmol) after 120 h at 180-200 °C as a colourless solid (0.013 g, 12%); data as above.



327 **335**

(c) Following general procedure 12, the title compound was obtained from ketone **327** (0.107 g, 0.50 mmol), methoxylamine hydrochloride (0.084 g, 1.00 mmol) and triethylamine (0.101 g, 1.00 mmol) as a colourless solid (0.031 g, 29%); data as above.

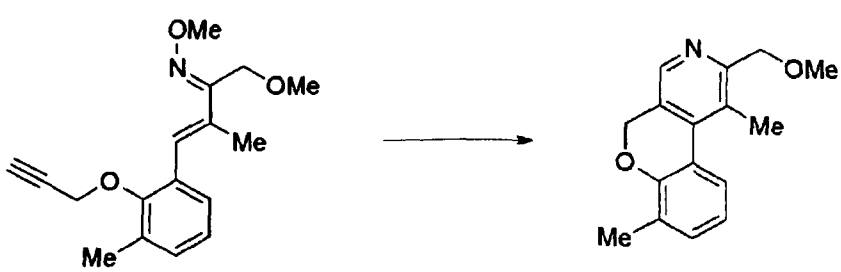
1,2,7-Trimethyl-5*H*-chromeno[3,4-*c*]pyridine 336



332 **336**

Following general procedure 11, the *title compound* was obtained from *O*-methyl oxime **332** (0.129 g, 0.50 mmol) after 16 h at 180 °C as a colourless solid (0.026 g, 26%), mp 74-76 °C (from ethyl acetate-hexane); (Found: MH^+, 226.1232. $C_{15}H_{15}NO$ + H requires 226.1226); ν_{max} ($CHCl_3$)/cm^{-1} 1590 (C=C), 1556 (C=C), 1464 (C=C), 1066 (C-O); δ_H (400 MHz; $CDCl_3$) 8.18 (1 H, s, H-4), 7.59 (1 H, d, J = 8.0 Hz, H-10), 7.20 (1 H, d, J = 7.2 H-8), 7.02 (1 H, t, J = 7.2 Hz, H-9), 4.95 (2 H, s, CH_2), 2.60 (3 H, s, Me), 2.53 (3 H, s, Me), 2.31 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 158.6 (C), 155.7 (C), 141.7 (CH), 137.2 (C), 131.8 (CH), 127.2 (C), 126.9 (C), 126.6 (C), 126.4 (CH), 122.1 (C), 120.8 (CH), 66.9 (CH_2), 23.9 (Me), 17.7 (Me), 16.0 (Me); *m/z* (ESI) *m/z* (ESI) 226 (MH^+, 100%).

2-Methoxymethyl-1,7-dimethyl-5*H*-chromeno[3,4-*c*]pyridine 337

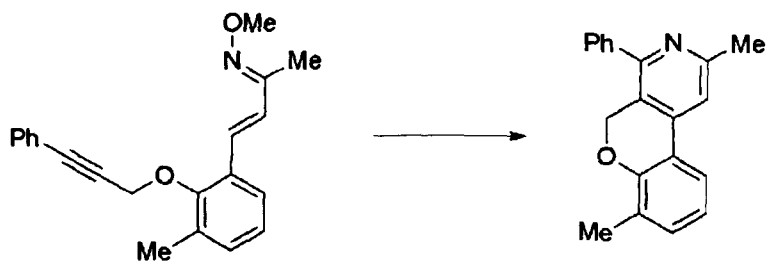


333 **337**

Following general procedure 11, the *title compound* was obtained from *O*-methyl oxime **333** (0.144 g, 0.50 mmol) after 16 h at 180 °C as a colourless solid (0.035 g, 27%), mp 50-52 °C (from ethyl acetate-hexane); (Found: MH^+, 256.1346. $C_{16}H_{17}NO_2$

+ H requires 256.1332); ν_{max} ($CHCl_3$)/cm^{-1} 1588 (C=C), 1556 (C=C), 1464 (C=C), 1094 (C-O); δ_H (400 MHz; $CDCl_3$) 8.30 (1 H, s, H-4), 7.65 (1 H, d, J = 7.9 Hz, H-10), 7.23 (1 H, d, J = 7.6 Hz, H-8), 7.04 (1 H, dd, J = 7.6 and 7.9 Hz, H-9), 5.00 (2 H, s, CH_2), 4.72 (2 H, s, CH_2), 3.48 (3 H, s, OMe), 2.64 (3 H, s, Me), 2.33 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 157.1 (C), 155.6 (C), 142.0 (CH), 138.1 (C), 132.1 (CH), 128.4 (C), 128.0 (C), 127.2 (C), 126.5 (CH), 121.9 (C), 120.9 (CH), 75.6 (CH_2), 66.8 (CH_2), 58.5 (Me), 16.8 (Me), 16.0 (Me); *m/z* (ESI) 270 (32%), 256 (MH^+, 100%).

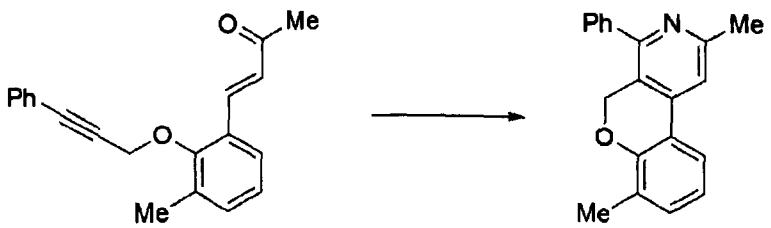
2,7-Dimethyl-4-phenyl-5*H*-chromeno[3,4-*c*]pyridine 344



340 **344**

(a) Following general procedure 11, the *title compound* was obtained from *O*-methyl oxime **340** (0.160 g, 0.50 mmol) after 16 h at 180 °C as a colourless solid (0.089 g, 62%), mp 148-150 °C (from ethyl acetate-hexane); (Found: MH^+, 288.1396. $C_{20}H_{17}NO$ + H requires 288.1383); ν_{max} ($CHCl_3$)/cm^{-1} 1595 (C=C), 1579 (C=C), 1560 (C=C), 1498 (C=C), 1471 (C=C), 1450 (C=C), 1420 (C=C), 1021 (C-O); δ_H (400 MHz; $CDCl_3$) 7.64 (1 H, d, J = 7.6 Hz, H-10), 7.51-7.44 (5 H, m, ArH), 7.42 (1 H, s, H-3), 7.22 (1 H, d, J = 7.5 Hz, H-8), 7.02 (1 H, dd, J = 7.5 and 7.6 Hz, H-9), 5.18 (2 H, s, CH_2), 2.69 (3 H, s, Me), 2.27 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 157.7 (C), 155.2 (C), 153.9 (C), 139.2 (C), 139.0 (C), 132.6 (CH), 129.1 (CH), 128.9 (CH), 128.5 (CH), 127.0 (C), 121.8 (CH), 121.7(CH), 121.3 (C), 120.8 (C), 114.9 (CH), 65.5 (CH_2), 24.8 (Me), 15.8 (Me); *m/z* (ESI) 288 (MH^+, 100%).

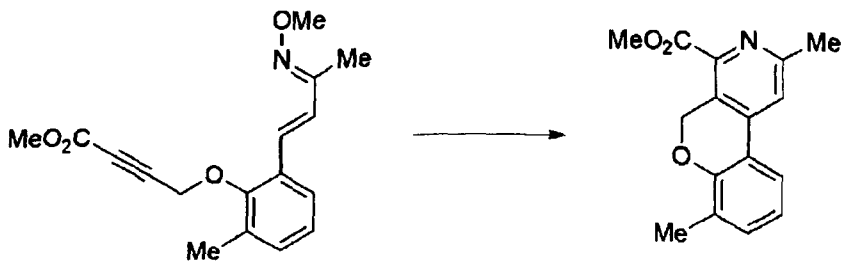
(b) Following general procedure 11, the title compound was obtained from *O*-methyl oxime **340** (0.151 g, 0.50 mmol) after 16 h at 140 °C as a colourless solid (0.055 g, 41%); data as above.



339 **344**

(c) Following general procedure 12, the title compound was obtained from ketone **339** (0.145 g, 0.50 mmol), methoxylamine hydrochloride (0.084 g, 1.00 mmol) and triethylamine (0.101 g, 1.00 mmol) as a colourless solid (0.053 g, 37%); data as above.

Methyl 2,7-dimethyl-5*H*-chromeno[3,4-*c*]pyridine-4-carboxylate 345



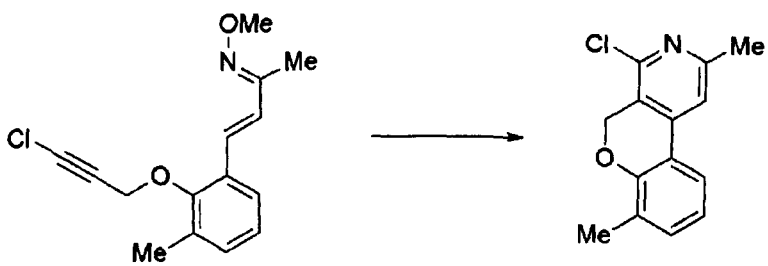
341 **345**

(a) Following general procedure 11, the *title compound* was obtained from *O*-methyl oxime **341** (0.090 g, 0.30 mmol) after 16 h at 180 °C as a colourless solid (0.040 g, 50%), mp 47-49 °C (from ethyl acetate-hexane); (Found: MH^+, 270.1129. $C_{16}H_{15}NO_3$ + H requires 270.1125); ν_{max} ($CHCl_3$)/cm^{-1} 1719 (C=O), 1597 (C=C), 1556 (C=C), 1472 (C=C), 1438 (C=C) 1087 (C-O); δ_H (400 MHz; $CDCl_3$) 7.56-7.55 (2 H, m, ArH), 7.21 (1 H, d, J = 7.3 Hz, H-8), 6.97 (1 H, dd, J = 7.3 and 8.1 Hz, H-9), 5.52 (2 H, s, CH_2), 4.01 (3 H, s, OMe), 2.67 (3 H, s, Me), 2.28 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$)

165.0 (C), 156.7 (C), 152.9 (C), 142.4 (C), 139.1 (C), 132.1 (CH), 126.1 (C), 125.7 (C), 120.6 (CH), 120.5 (CH), 118.4 (C), 117.8 (CH), 63.9 (CH_2), 51.9 (Me), 23.6 (Me), 14.6 (Me); *m/z* (ESI) 292 (MNa^+, 28%), 284 (41), 270 (MH^+, 100).

(b) Following general procedure 11, the title compound was obtained from *O*-methyl oxime **341** (0.151 g, 0.50 mmol) after 16 h at 140 °C as a colourless solid (0.055 g, 41%); data as above.

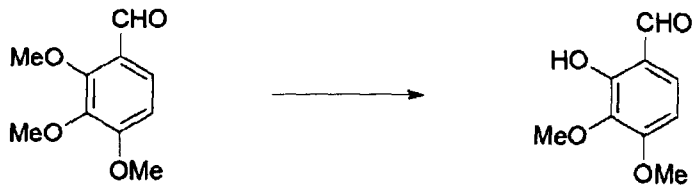
4-Chloro-2,7-dimethyl-5*H*-chromeno[3,4-*c*]pyridine 346



342 **346**

Following general procedure 11, the *title compound* was obtained from *O*-methyl oxime **342** (0.139 g, 0.50 mmol) after 16 h at 180 °C as a colourless solid (0.020 g, 16%), mp 110-112 °C (from ethyl acetate-hexane); (Found: MH^+, 246.0683. $C_{14}H_{12}{}^{35}ClNO$ + H requires 246.0680); ν_{max} ($CHCl_3$)/cm^{-1} 1600 (C=C), 1548 (C=C), 1448 (C=C), 1056 (C-O); δ_H (400 MHz; $CDCl_3$) 7.54 (1 H, d, J = 7.7 Hz, H-10), 7.35 (1 H, s, H-1), 7.23 (1 H, d, J = 7.7 Hz, H-8), 6.99 (1 H, t, J = 7.7 Hz, H-9), 5.26 (2 H, s, CH_2), 2.59 (3 H, s, Me), 2.28 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 158.6 (C), 153.7 (C), 146.5 (C), 141.4 (C), 133.4 (CH), 127.3 (C), 121.8 (CH), 121.7 (CH), 121.4 (C), 119.2 (C), 115.0 (CH), 64.7 (CH_2), 24.3 (Me), 15.8 (Me); *m/z* (ESI) 248/246 (MH^+, 30/100%). Also obtained was 2,7-dimethyl-5*H*-chromeno[3,4-*c*]pyridine **240** (30%).

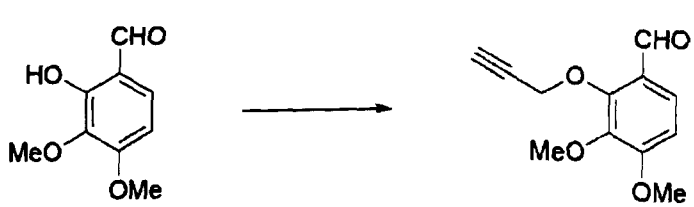
2-Hydroxy-3,4-dimethoxybenzaldehyde[138] 279



347 **279**

To a solution of 2,3,4-trimethoxybenzaldehyde **347** (75.0 g, 0.382 mol) in benzene (1000 mL) was added aluminium trichloride (53.5 g, 0.401 mol). The reaction mixture was heated at reflux for 6 h then cooled to room temperature. Ice/water (1000 mL) and concentrated hydrochloric acid (200 mL) were added and the reaction mixture stirred for 30 min. The organics was separated and the aqueous layer was extracted with ether (6 × 1000 mL). The combined organics were washed with water (2000 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the title compound as a colourless solid (49.5 g, 71%), mp 70 - 71 °C (lit.,[138] mp 69 - 70 °C); δ_H (400 MHz; $CDCl_3$) 11.2 (1 H, s, CHO), 9.7 (1 H, s, OH), 7.29 (1 H, d, J = 8.7 Hz, ArH), 6.60 (1 H, d, J = 8.7 Hz, ArH), 3.95 (3 H, s, OMe), 3.90 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 195.0 (CH), 159.4 (C), 155.7 (C), 136.1 (C), 130.3 (CH), 116.5 (C), 104.1 (CH), 60.7 (OMe), 56.2 (OMe).

3,4-Dimethoxy-2-(prop-2-ynyloxy)benzaldehyde 318



279 **318**

Following general procedure 6, the *title compound* was obtained from 2-hydroxy-3,4-dimethoxybenzaldehyde **279** (36.4 g, 0.2200 mol), potassium carbonate (41.4 g, 0.300

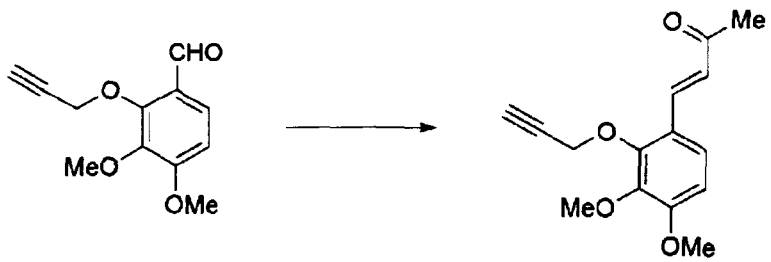
mol) and propargyl chloride (71.6 mL, 1.00 mol) as a pale yellow solid (36.2 g, 82%), mp 106-107 °C (from ethanol); (Found: MH^+, 221.0822. $C_{12}H_{12}O_4$ + H requires 221.0814); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C-H), 2125 (C≡C), 1678 (C=O), 1592 (C=C), 1498 (C=C), 1460 (C=C); δ_H (400 MHz; $CDCl_3$) 10.3 (1 H, d, J = 0.7 Hz, CHO), 7.64 (1 H, d, J = 8.8 Hz, ArH), 6.81 (1 H, d, J = 8.8 Hz, ArH), 4.91 (2 H, d, J = 2.4 Hz, CH_2), 3.94 (3 H, s, OMe), 3.89 (3 H, s, OMe), 2.50 (1 H, t, J = 2.4 Hz, C≡CH); δ_C (75 MHz; $CDCl_3$) 189.2 (C), 159.0 (CH), 154.2 (C), 141.7 (C), 129.0 (C), 128.2 (C), 124.5 (C), 123.7 (CH), 108.3 (CH), 61.4 (OMe), 61.1 (OMe), 56.2 (CH_2); *m/z* (EI) 221 (MH^+, 100%), 193 (37), 189 (80).

Diethyl 1-methyl-2-oxopropylphosphonate[133] 319

391 **319**

Following general procedure 13, the title compound was obtained from diethyl ethylphosphonate (10.0 g, 60.2 mmol) and ethyl acetate (5.83 g, 66.2 mmol) as a colourless oil (11.4 g, 91%); ν_{max} ($CHCl_3$)/cm^{-1} 1714 (C=O), 1302 (P=O); δ_H (400 MHz; $CDCl_3$) 4.16 - 4.07 (4 H, m, 2 × CH_2), 3.25 - 3.13 (1 H, dq, J = 7.1 and 25.6 Hz, CH), 2.32 (3 H, s, CH_3), 1.37 - 1.29 (9 H, m, 3 × CH_3); δ_C (100 MHz; $CDCl_3$) 203.9 (d, $^2J_{C\text{-}P}$ = 3.7 Hz, C=O), 62.6 (d, $^2J_{C\text{-}P}$ = 6.7 Hz, CH_2), 62.5 (d, $^2J_{C\text{-}P}$ = 6.7 Hz, CH_2), 47.5 (d, $^1J_{C\text{-}P}$ = 126.9 Hz, CH), 30.4 (Me), 16.4 (Me), 16.3 (Me), 10.8 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, Me).

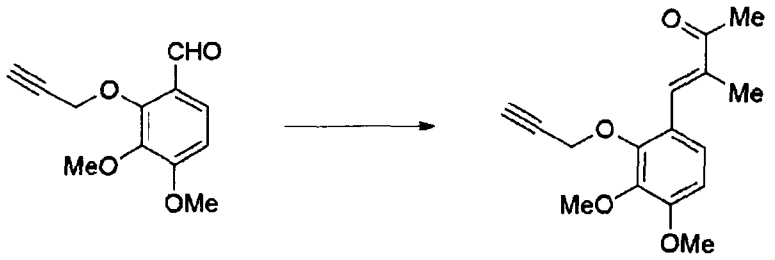
4-(3,4-Dimethoxy-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one 348



318 **348**

Following general procedure 7, the *title compound* was obtained from 3,4-dimethoxy-2-(prop-2-ynyloxy)benzaldehyde **318** (0.440 g, 2.00 mmol) and diethyl 2-oxopropylphosphonate (0.583 g, 3.00 mmol) as a colourless solid (0.478 g, 92%), mp 71-72 °C (from ethanol); (Found: MH^+, 261.1122. $C_{15}H_{16}O_4$ + H requires 261.1126); ν_{max} ($CHCl_3$)/cm^{-1} 3306 (alkyne C-H), 2126 (C≡C), 1667 (C=O), 1642 (C=C), 1594 (C=C), 1496 (C=C), 1456 (C=C), 1096 (C-O); δ_H (400 MHz; $CDCl_3$) 7.90 (1 H, d, J = 16.6 Hz, C=CH), 7.35 (1 H, d, J = 8.8 Hz, ArH), 6.76 (1 H, d, J = 8.8 Hz, ArH), 6.64 (1 H, d, J = 16.6 Hz, C=CH), 4.83 (2 H, d, J = 2.4 Hz, CH_2), 3.91 (3 H, s, OMe), 3.88 (3 H, s, OMe), 2.51 (1 H, t, J = 2.4 Hz, C≡CH), 2.40 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 199.1 (C), 155.6 (C), 150.9 (C), 142.3 (C), 138.9 (CH), 126.6 (CH), 122.4 (CH), 122.2 (C), 108.5 (CH), 78.8 (C≡CH), 76.0 (C≡CH), 61.1 (CH_2), 61.0 (CH_3), 56.1 (CH_3), 26.7 (CH_3); *m/z* (ESI) 283 (MNa^+, 71%), 261 (MH^+, 100).

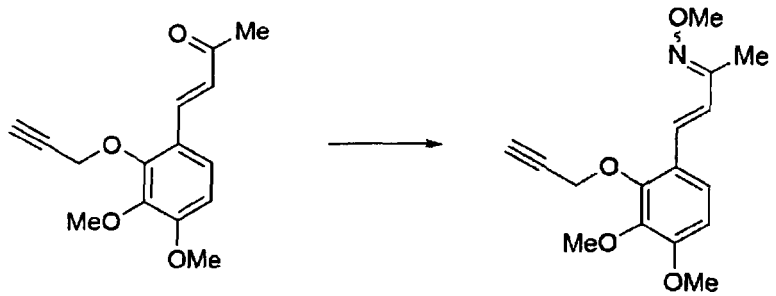
4-(3,4-Dimethoxy-2-(prop-2-ynyloxy)phenyl)-3-methylbut-3-en-2-one 349



318 **349**

Following general procedure 7, the *title compound* was obtained from 3,4-dimethoxy-2-(prop-2-ynyloxy)benzaldehyde **318** (0.440 g, 2.00 mmol) and diethyl 1-methyl-2-oxopropylphosphonate **319** (0.625 g, 3.00 mmol) as a colourless oil (0.545 g, 99%); (Found: MNa^+, 297.1097. $C_{16}H_{18}O_4$ + Na requires 297.1097); ν_{max} ($CHCl_3$)/cm^{-1} 3306 (alkyne C-H), 1659 (C=O), 1625 (C=C), 1595 (C=C), 1495 (C=C), 1455 (C=C), 1365 (N=O), 1099 (C-O); δ_H (400 MHz; $CDCl_3$) 7.83 (1 H, s, C=CH), 7.17 (1 H, d, J = 8.7 Hz, ArH), 6.76 (1 H, d, J = 8.7 Hz, ArH), 4.79 (2 H, d, J = 2.4 Hz, CH_2), 3.92 (3 H, s, OMe), 3.90 (3 H, s, OMe), 2.49 (3 H, s, Me), 2.01 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 200.6 (C), 154.2 (C), 150.4 (C), 142.2 (C), 136.9 (C), 135.6 (CH), 125.0 (C), 123.5 (CH), 107.7 (CH), 79.1 (C≡CH), 75.5 (C≡CH), 61.0 (OMe), 56.1 (OMe), 29.7 (CH_2), 25.8 (Me), 12.9 (Me); *m/z* (ESI) 297 (MNa^+, 100%), 275 (MH^+, 79), 243 (22).

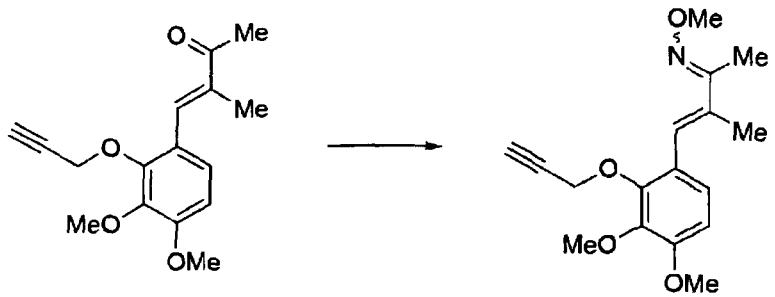
(3*E*)-4-(3,4-Dimethoxy-2-(prop-2-ynyloxy)phenyl)but-3-en-2-one *O*-methyl oxime 350



348 **350**

Following general procedure 9, the *title compound* was obtained from α,β-unsaturated ketone **348** (0.195 g, 0.75 mmol), methoxylamine hydrochloride (0.078 g, 0.938 mmol) and sodium acetate trihydrate (0.107 g, 0.788 mmol) as a colourless oil (0.217 g, 100%); (Found: MH^+, 290.1382. $C_{16}H_{19}NO_4$ + H requires 290.1387); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C-H), 2126 (C≡C), 1598 (C=C), 1497 (C=C), 1457 (C=C), 1097 (C-O); δ_H (400 MHz; $CDCl_3$) 7.31 (1 H, d, J = 8.8 Hz, ArH), 7.27 (1 H, d, J = 16.4 Hz, C=CH), 6.72 (1 H, d, J = 16.4 Hz, C=CH), 6.71 (1 H, d, J = 8.8 Hz, ArH), 4.77 (2 H, d, J = 2.4 Hz, CH_2), 3.95 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.87 (3 H, s, OMe), 2.50 (1 H, t, J = 2.4 Hz, C≡CH), 2.09 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.3 (C), 153.7 (C), 149.7 (C), 142.3 (C), 127.5 (CH), 124.7 (CH), 124.3 (C), 120.4 (CH), 108.5 (CH), 79.1 (C≡CH), 75.6 (C≡CH), 61.8 (OMe), 61.1 (CH_2), 60.9 (OMe), 56.0 (OMe), 10.1 (Me); *m/z* (ESI) 312 (MNa^+, 100%), 290 (MH^+, 38).

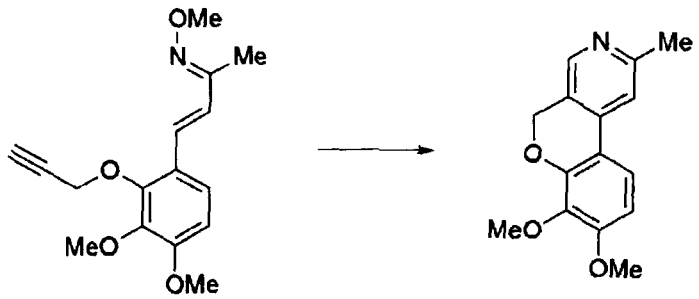
(3*E*)-4-(3,4-Dimethoxy-2-(prop-2-ynyloxy)phenyl)-3-methylbut-3-en-2-one *O*-methyl oxime 351



349 **351**

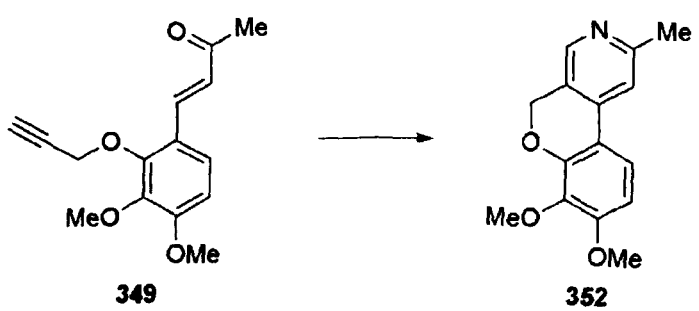
Following general procedure 9, the *title compound* was obtained from α,β-unsaturated ketone **349** (0.206 g, 0.75 mmol), methoxylamine hydrochloride (0.078 g, 0.938 mmol) and sodium acetate trihydrate (0.107 g, 0.788 mmol) as a colourless oil (0.228 g, 100%); Found: MH^+, 304.1530. $C_{17}H_{21}NO_4$ + H requires 304.1543); ν_{max} ($CHCl_3$)/cm^{-1} 3308 (alkyne C-H), 2126 (C≡C), 1599 (C=C), 1495 (C=C), 1455 (C=C), 1097 (C-O); δ_H (400 MHz; $CDCl_3$) 7.03 (1 H, s, C=CH), 7.02 (1 H, d, J = 8.8 Hz, ArH), 6.72 (1 H, d, J = 8.8 Hz, ArH), 4.71 (2 H, d, J = 2.4 Hz, CH_2), 3.95 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.88 (3 H, s, OMe), 2.47 (1 H, t, J = 2.4 Hz, C≡CH), 2.13 (3 H, s, Me), 2.05 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 157.2 (C), 152.9 (C), 150.0 (C), 142.2 (C), 134.4 (C), 125.9 (CH), 125.0 (CH), 124.8 (C), 107.5 (CH), 79.3 (C≡C), 75.1 (C≡C), 61.8 (OMe), 61.0 (OMe), 60.4 (CH_2), 56.0 (OMe), 14.4 (Me),10.8 (Me); *m/z* (ESI) 326 (MNa^+, 100%), 304 (MH^+, 26).

7,8-Dimethoxy-2-methyl-5*H*-chromeno[3,4-*c*]pyridine 352



349 **352**

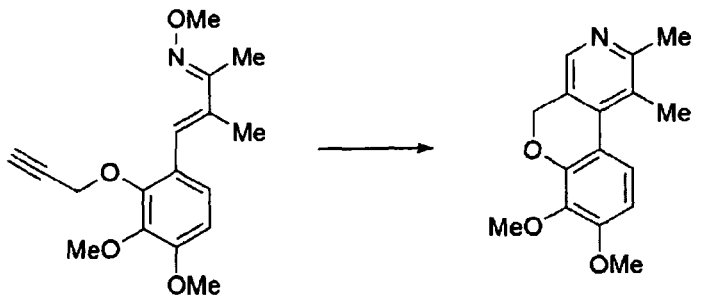
a. Following general procedure 11, the *title compound* was obtained from *O*-methyl oxime **349** (0.100 g, 0.346 mmol) as a colourless solid (0.040 g, 45%), mp 115-117 °C (from dichloromethane-hexane); (Found: MH^+, 258.1124. $C_{15}H_{15}NO_3$ + H requires 258.1125); ν_{max} ($CHCl_3$)/cm^{-1} 1607 (C=C), 1508 (C=C), 1488 (C=C), 1081 (C-O); δ_H (400 MHz; $CDCl_3$) 8.30 (1 H, s, ArH), 7.46 (1 H, d, J = 8.8 Hz, ArH), 7.33 (1 H, s, ArH), 6.68 (1 H, d, J = 8.8 Hz, ArH), 5.17 (2 H, s, CH_2), 3.93 (3 H, s, OMe), 3.91 (3 H, s, OMe), 2.60 (Me); δ_C (100 MHz; $CDCl_3$) 158.6 (C), 155.2 (C), 145.0 (CH), 138.0 (C), 122.3 (C), 119.0 (CH), 115.2 (C), 114.9 (CH), 106.0 (CH), 66.3 (CH_2), 61.2 (OMe), 56.1 (OMe), 24.6 (Me); *m/z* (ESI) 258 (MH^+, 100%), 242 (16).



349 **352**

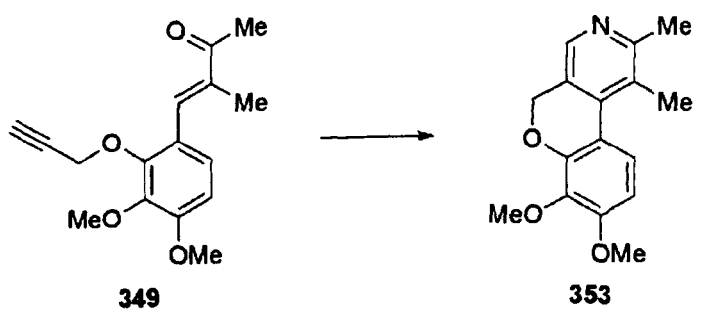
b. Following general procedure 12, the *title compound* was obtained from ketone **348** (0.052, 0.200 mmol), methoxylamine hydrochloride (0.033 g, 0.400 mmol) and triethylamine (0.040 g, 0.400 mmol) as a colourless solid (0.028 g, 54%); data as above.

7,8-Dimethoxy-1,2-dimethyl-5*H*-chromeno[3,4-*c*]pyridine 353



351 **353**

a) Following general procedure 11, the *title compound* was obtained from *O*-methyl oxime **351** (0.100 g, 0.330 mmol) as a colourless solid (0.043 g, 48%), mp 131-133 °C (from dichloromethane-hexane); (Found: MH^+, 272.1272. $C_{16}H_{17}NO_3$ + H requires 272.1281); ν_{max} ($CHCl_3$)/cm^{-1} 1592 (C=C), 1552 (C=C), 1506 (C=C), 1467 (C=C), 1104 (C-O); δ_H (400 MHz; $CDCl_3$) 8.18 (1 H, s, ArH), 7.46 (1 H, d, J = 8.8 Hz, ArH), 6.69 (1 H, d, J = 8.8 Hz, ArH), 4.98 (2 H, s, CH_2), 3.91 (3 H, s, OMe), 3.90 (3 H, s, OMe), 2.58 (3 H, s, Me), 2.50 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 158.5 (C), 154.1 (C), 151.3 (C), 141.7 (CH), 138.3 (C), 136.9 (C), 126.0 (C), 125.9 (C), 123.9 (CH), 117.0 (C), 105.0 (CH), 67.5 (CH_2), 61.3 (OMe), 56.1 (OMe), 23.8 (Me), 17.7 (Me); *m/z* (ESI) 272 (MH^+, 100%).



349 **353**

b. Following general procedure 12, the *title compound* was obtained from α,β-unsaturated ketone **349** (0.055, 0.200 mmol), methoxylamine hydrochloride (0.033 g,

0.400 mmol) and triethylamine (0.040 g, 0.400 mmol) as a colourless solid (0.030 g, 56%); data as above.

6-Methoxyquinoline-*N*-oxide 354

299 **354**

To a solution of 6-methoxyquinoline **299** (50.0 g, 314 mmol) in glacial acetic acid (315 mL) was added 30% hydrogen peroxide (50 mL). The reaction mixture was heated at 80 °C for 3 h, then further 30% hydrogen peroxide (50 mL) was added. Stirring was continued at 80 °C for 3 h. The reaction mixture was allowed to cool to room temperature, basified with sodium hydroxide (2 M) and extracted with dichloromethane (5 × 1000 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a colourless solid (47.2 g, 85%), mp 109 - 110 °C (lit.,[140] mp 110 - 112 °C); δ_H (400 MHz; $CDCl_3$) 8.64 (1 H, d, J = 9.5 Hz, ArH), 8.39 (1 H, dd, J = 6.0 and 0.7 Hz, ArH), 7.62 (1 H, d, J = 8.5 Hz, ArH), 7.36 (1 H, dd, J = 9.5 and 2.6 Hz, ArH), 7.24 (1 H, dd, J = 8.5 and 6.0 Hz, ArH), 7.09 (1 H, d, J = 2.6 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 159.4 (C), 137.1 (C), 133.8 (CH), 132.0 (C), 125.2 (CH), 122.8 (CH), 121.5 (CH), 121.4 (CH), 105.8 (CH), 55.7 (OMe).

2-Chloro-6-methoxyquinoline 355

354 **355**

6-Methoxyquinoline-*N*-oxide **354** (20.0 g, 114 mmol) was added portionwise to phosphorus oxychloride (100 mL) at 0 °C. The reaction mixture was heated at 100 °C for 1 h and cooled to room temperature. The reaction mixture was then poured into sodium hydroxide (5 M; 1500 mL). The resulting precipitate was filtered off and washed with dichloromethane (1000 mL). The filtrate was extracted with dichloromethane (5 × 1000 mL). The combined organics were washed with water (2000 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the title compound as a colourless solid (11.0 g, 50%), mp 105 - 106 °C (lit.,[140] mp 106.5 - 107.5 °C); δ_H (400 MHz; $CDCl_3$) 7.85 (1 H, d, J = 8.9 Hz, ArH), 7.82 (1 H, d, J = 9.5 Hz, ArH), 7.29 (1 H, dd, J = 2.6 Hz and 9.2 Hz, ArH), 7.21 (1 H, d, J = 8.5 Hz, ArH), 6.93 (1 H, d, J = 2.4 Hz, ArH), 3.83 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 185.1 (C), 148.0 (C), 143.8 (C), 137.6 (CH), 129.9 (CH), 127.9 (C), 123.1 (CH), 122.5 (CH), 105.3 (CH), 55.6 (OMe).

2-Iodo-6-methoxyquinoline 356

355 **356**

To a solution of 2-chloro-6-methoxyquinoline **355** (22.0 g, 114 mmol) and sodium iodide (85.4 g, 570 mmol) in acetonitrile (450 mL) was added hydrochloric acid (5 M;

22 mL). The reaction mixture was heated under reflux for 17 h and concentrated *in vacuo*. Water (1000 mL) was added and the aqueous phase neutralised with saturated sodium hydrogen carbonate. The aqueous phase was then extracted with dichloromethane (4 × 1000 mL) and chloroform (4 × 1000 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with dichloromethane, to afford the title compound as a colourless solid (29.2 g, 90%), mp 144 - 145 °C (lit.,[140] mp 146 - 147 °C); δ_H (400 MHz; $CDCl_3$) 7.93 (1 H, d, J = 9.2 Hz, H-8), 7.66 (2 H, m, H-3/4), 7.34 (1 H, dd, J = 9.2 and 2.8 Hz, H-7), 7.02 (1 H, d, J = 2.8 Hz, H-5), 3.92 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 158.1 (C), 145.8 (C), 136.0 (CH), 132.1 (CH), 130.3 (CH), 128.3 (C), 105.3 (CH), 55.6 (OMe).

2-Iodo-6-methoxy-5-nitroquinoline 317

356 **317**

Three flasks were each charged with 2-iodo-6-methoxyquinoline **356** (9.25 g, 32.4 mmol) in concentrated sulfuric acid (35.5 mL) at 0 °C. To each reaction was added nitric acid (70%; 6.5 mL) dropwise over 30 min. Stirring was continued at 0 °C for 45 min. Each reaction mixture was poured onto ice (350 mL), basified with sodium hydroxide (2 M) and extracted with dichloromethane (3 × 500 mL) and chloroform (3× 500 mL). The combined organics were washed with water (500 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was combined and filtered through a pad of silica gel, eluting with dichloromethane, to afford the title compound as a pale yellow solid (16.6 g, 52%), mp 173 - 174 °C (lit.,[140] mp 171.5 - 173 °C); δ_H

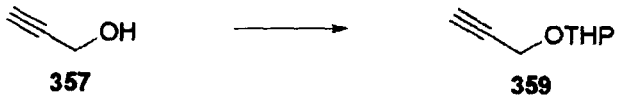
(400 MHz; $CDCl_3$) 8.21 (1 H, d, J = 9.5 Hz, H-4), 7.83 (1 H, d, J = 8.9 Hz, H-8), 7.69 (1 H, d, J = 8.9 Hz, H-7), 7.57 (1 H, d, J = 9.5 Hz, H-3), 4.08 (3 H , s, OMe); δ_C (100 MHz; $CDCl_3$) 149.6 (C), 143.4 (C), 134.4 (CH), 133.5 (CH), 132.3 (C), 130.3 (CH), 120.6 (C), 117.5 (C), 117.0 (CH), 57.3 (OMe).

Prop-2-ynyl-4-methylbenzenesulfonate[141] 358

357 **358**

To a solution of propargyl alcohol **357** (1.46 mL, 25.0 mmol) and *para*-toluenesulfonyl chloride (5.72 g, 30.0 mmol) in ether (100 mL) at - 5 °C was added potassium hydroxide (14.0 g, 250 mmol) portionwise. Stirring was continued at - 5 °C for 2 h. The reaction mixture was poured into water (100 mL) and extracted with ether (2 × 100 mL). The combined organics were washed with water (2 × 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9 to 1:4), to afford the title compound as a colourless oil (4.44 g, 84%); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C-H), 2135 (C≡C), 1598 (C=C), 1494 (C=C), 1452 (C=C), 1368 (S=O), 1096 (S=O); δ_H (400 MHz; $CDCl_3$) 7.83 (2 H, d, J = 8.4 Hz, ArH), 7.36 (2 H, d, J = 8.4 Hz, ArH), 4.71 (2 H, d, J = 2.5 Hz, CH_2), 2.48 (1 H, t, J = 2.5 Hz, C≡CH), 2.47 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 145.2 (C), 132.9 (C), 129.9 (CH), 128.1 (CH), 75.4 (C≡<u>C</u>H), 57.3 (CH_2), 21.7 (Me).

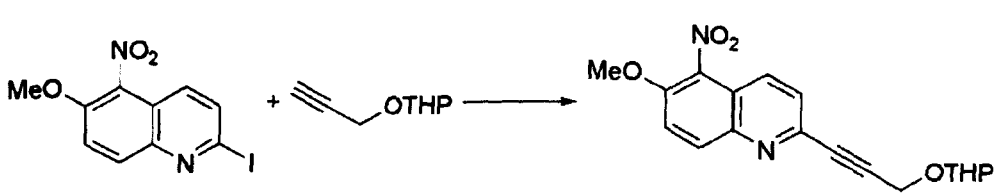
2-[(Prop-2-yn-1-yl)oxy]tetrahydropyran[142] 359



357 359

To a solution of propargyl alcohol **357** (1.74 mL, 30.0 mmol) and 2*H*-3,4-dihydropyran (3.28 mL, 36.0 mmol) in dichloromethane (75 mL) was added *para*-toluenesulfonic acid (0.050 g, 0.263 mmol). The reaction mixture was stirred for 20 h and poured into water (200 mL). The aqueous layer was separated and extracted with dichloromethane (150 mL). The combined organics were washed with water (200 mL) and saturated brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:49 to 1:19), to afford the title compound as a colourless oil (3.12 g, 74%); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C-H), 2122 (C≡C), 1119 (C-O), 1077 (C-O), 1056 (C-O), 1042 (C-O); δ_H (400 MHz; $CDCl_3$) 4.83 (1 H, t, J = 3.3 Hz, CH), 4.30 (1 H, dd, J = 15.7 and 2.4 Hz, CH), 4.24 (1 H, dd, J = 15.7 and 2.4 Hz, CH), 3.88-3.82 (1 H, m, CH), 3.57-3.52 (1 H, m, CH), 2.42 (1 H, t, J = 2.4 Hz, CH), 1.90-1.49 (6 H, m, 3 × CH_2); δ_C (100 MHz; $CDCl_3$) 96.9 (CH), 79.8 (C≡CH), 74.0 (C≡CH), 62.0 (CH_2), 54.0 (CH_2), 30.2 (CH_2), 25.3 (CH_2), 19.0 (CH_2).

6-Methoxy-5-nitro-2-(3-(tetrahydro-2*H*-pyran-2-yloxy)prop-1-ynyl)quinoline 362

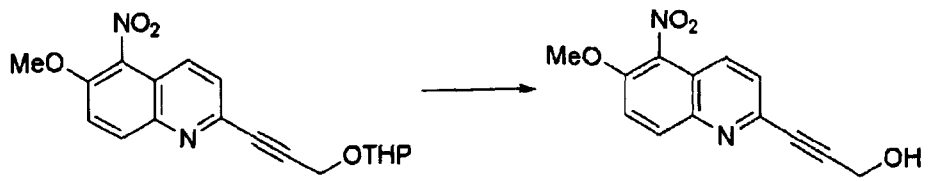


317 359 362

Following general procedure 12, the *title compound* was obtained from 2-iodo-6-methoxy-5-nitroquinoline **317** (1.10 g, 3.33 mmol) and 2-[(prop-2-yn-1-yl)oxy]tetrahydropyran **359** (0.700 g, 5.00 mmol) as a pale orange solid (0.912 g,

80%), mp 107-109 °C (from ethanol); (Found: MH^+, 343.1281. $C_{18}H_{18}N_2O_5$ + H requires 343.1299); ν_{max} ($CHCl_3$)/cm^{-1} 1628 (C=C), 1595 (C=C), 1550 (N=O), 1494 (C=C), 1460 (C=C), 1356 (N=O), 1120 (C-O), 1078 (C-O); δ_H (400 MHz; $CDCl_3$) 8.15 (1 H, d, J = 9.5 Hz, ArH), 7.96 (1 H, d, J = 8.8 Hz, ArH), 7.55 (1 H, d, J = 8.8 Hz, ArH), 7.54 (1 H, d, J = 9.5 Hz, ArH), 4.87 (1 H, t, J = 3.4 Hz, CH), 4.55 (1 H, d, J = 16.1 Hz, C≡CCH), 4.49 (1 H, d, J = 16.1 Hz, C≡CCH), 4.03 (3 H, s, OMe), 3.87-3.81 (1 H, m, CH), 3.56-3.51 (1 H, m, CH), 1.82-1.52 (6 H, m, 3 × CH_2); δ_C (100 MHz; $CDCl_3$) 149.7 (C), 142.2 (C), 142.0 (C), 134.4 (C), 133.9 (CH), 129.4 (CH), 126.6 (CH), 120.2 (C), 116.8 (CH), 97.2 (CH), 87.3 (C), 84.8 (C), 62.0 (CH_2), 57.2 (CH_2), 54.5 (CH_2), 30.2 (CH_2), 25.3 (CH_2), 18.9 (CH_2); *m/z* (ESI) 365 (20%), 343 (MH^+, 100), 241 (21).

3-(6-Methoxy-5-nitroquinolin-2-yl)prop-2-yn-1-ol 360

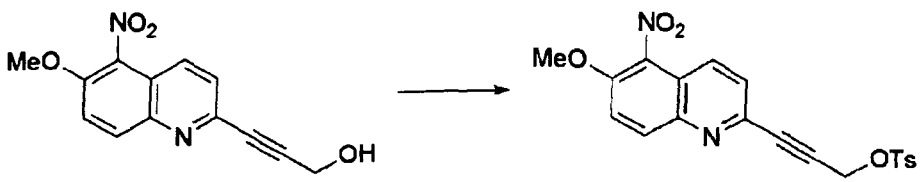


362 **360**

To a solution of 6-methoxy-5-nitro-2-(3-(tetrahydro-2*H*-pyran-2-yloxy)prop-1-ynyl)quinoline **362** (0.850 g, 2.48 mmol) in ethanol (35 mL) was added *para*-toluenesulfonic acid (0.095 g, 0.496 mmol) in one portion. The reaction mixture was stirred at room temperature for 4 h and concentrated *in vacuo*. The residue was partitioned between water (100 mL) and chloroform (3 × 250 mL). The combined organics were washed with saturated sodium hydrogen carbonate (250 mL) and saturated brine (250 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as an orange solid (0.626 g, 98%), mp 223-225 °C with decomposition

(from ethanol); (Found: MH^+, 259.0707. $C_{13}H_{10}N_2O_4$ + H requires 259.0724); ν_{max} ($CHCl_3$)/cm^{-1} 3696 (O-H), 3606 (O-H), 1628 (C=C), 1600 (C=C), 1494 (C=C), 1459 (C=C), 1356 (N=O), 1100 (C-O); δ_H (400 MHz; $CDCl_3$) 8.23 (1 H, d, J = 9.5 Hz, ArH), 8.07 (1 H, d, J = 9.4 Hz, ArH), 7.95 (1 H, d, J = 9.6 Hz, ArH), 7.69 (1 H, d, J = 8.8 Hz, ArH), 5.51 (1 H, br s, OH), 4.39 (2 H, s, CH_2), 4.08 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 149.4 (C), 141.7 (C), 141.5 (C), 133.6 (CH), 129.3 (CH), 126.6 (CH), 119.2 (C), 118.3 (CH), 96.6 (C), 91.2 (C), 83.3 (C), 57.5 (Me), 49.3 (CH_2); *m/z* (ESI) 365 (17%), 343 (76), 281 (19), 279 (28), 259 (MH^+, 100), 241 (19).

3-(6-Methoxy-5-nitroquinolin-2-yl)prop-2-ynyl 4-methylbenzenesulfonate 361

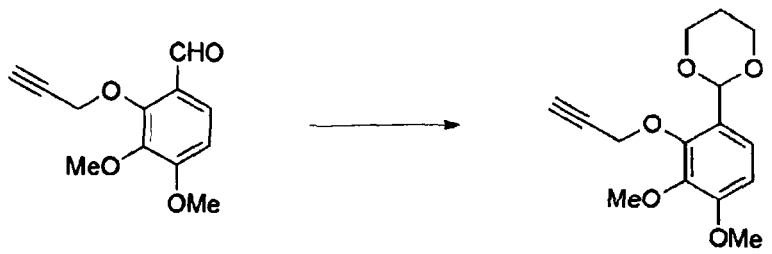


360 **361**

To a suspension of sodium hydride (0.010 g, 0.260 mmol) in THF (3 mL) at 0 °C was added 3-(6-methoxy-5-nitroquinolin-2-yl)prop-2-yn-1-ol **360** (0.052 g, 0.200 mmol) in one portion. The reaction mixture was allowed to warm to room temperature, stirred for 30 min then cooled back to 0 °C. *Para*-toluenesulfonyl chloride (0.046 g, 0.240 mmol) was added, and the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was removed *in vacuo*, and the residue was dissolved in ethyl acetate (50 mL) and washed with water (3 × 25 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9 to 1:4) to afford the *title compound* as a colourless solid (0.065 g, 79%), mp 138-140 °C (from dichlormethane-hexane); (Found: MH^+, 413.0798. $C_{20}H_{16}N_2O_6S$ + H requires 413.0802); δ_H (400 MHz; $CDCl_3$) 8.23 (1 H, d, J = 9.2 Hz, ArH), 8.03 (1 H, d, J = 8.0

Hz, ArH), 7.89 (2 H, d, J = 6.8 Hz, ArH), 7.62 (1 H, d, J = 9.2 Hz, ArH), 7.42 (1 H, d, J = 8.8 Hz, ArH), 7.35 (2 H, d, J = 8.0 Hz, ArH), 5.01 (2 H, s. CH_2), 4.10 (3 H, s, OMe), 2.40 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 150.1 (C), 145.4 (C), 141.9 (C), 140.9 (C), 134.3 (C), 134.0 (CH), 132.9 (C), 130.0 (CH), 129.5 (CH), 128.2 (CH), 126.3 (CH), 120.5 (C), 117.2 (CH), 87.4 (C≡C), 82.0 (C≡C), 57.8 (CH_2), 57.3 (OMe), 21.7 (Me); *m/z* (ESI) 435 (MNa^+, 100%), 413 (MH^+, 76).

2-(3,4-Dimethoxy-2-(prop-2-ynyloxy)phenyl)-1,3-dioxane 364

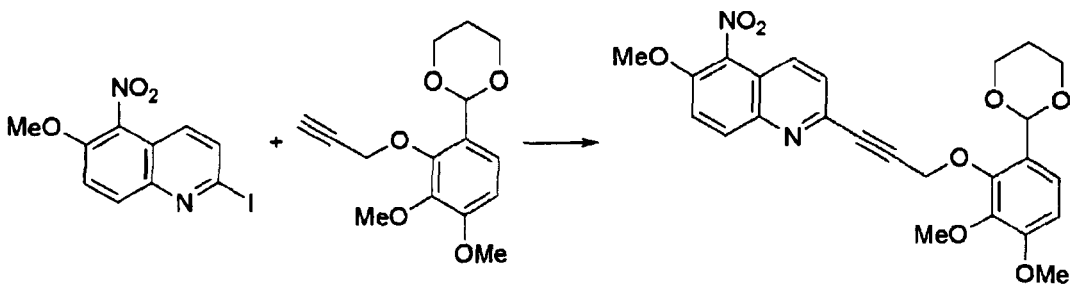


318 **364**

To a solution of 3,4-dimethoxy-2-(prop-2-ynyloxy)benzaldehyde **318** (34.1 g, 155 mmol) and *para*-toluenesulfonic acid (250 mg) in toluene (750 mL) was added 1,3-propanediol (17.7 g, 233 mmol). The reaction mixture was heated under reflux in a Dean-Stark apparatus for 42 h. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the *title compound* as a colourless solid (39.0 g, 90%), mp 59-60 °C (from ethanol); (Found: MH^+, 279.1220. $C_{15}H_{18}O_5$ + H requires 279.1232); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C-H), 1605 (C=C), 1500 (C=C), 1462 (C=C), 1096 (C-O), 1053 (C-O); δ_H (400 MHz; $CDCl_3$) 7.32 (1 H, d, J = 8.7 Hz, ArH), 6.74 (1 H, d, J = 8.7 Hz, ArH), 5.84 (1 H, s, CH), 4.76 (2 H, d, J = 2.4 Hz, CH_2), 4.27 -4.23 (2 H, m, CH_2), 4.06 - 3.99 (2 H, m, CH_2), 3.87 (3 H, s, OMe), 3.86 (3 H, s, OMe), 2.53 (1 H, t, J = 2.4 Hz, C≡CH), 2.29 - 2.27 (1 H, m, CH), 1.46 - 1.41 (1 H, m, CH); δ_C (100

MHz; $CDCl_3$) 154.0 (C), 149.2 (C), 141.8 (C), 125.8 (C), 121.5 (CH), 108.3 (CH), 97.5 (CH), 79.3 (C≡CH), 75.1 (C≡CH), 67.6 (CH_2), 61.2 (CH_2), 61.0 (CH_3), 56.1 (CH_3), 25.8 (CH_3); *m/z* (ESI) 301 (MNa^+, 34%), 279 (MH^+, 100).

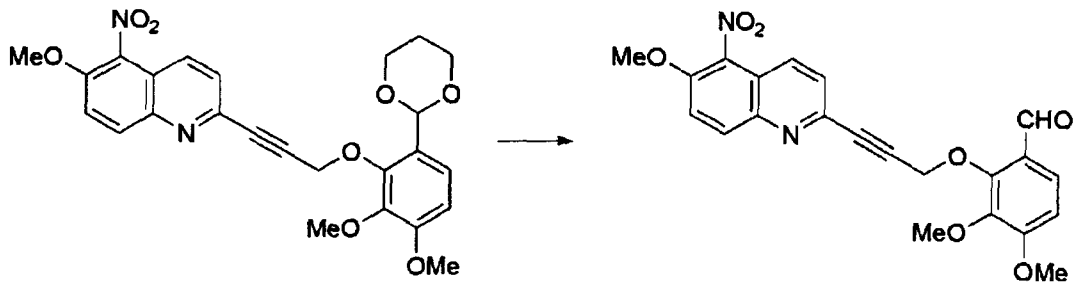
(3-(6-(1,3-Dioxan-2-yl)-2,3-dimethoxyphenoxy)prop-1-ynyl)-6-methoxy-5-nitroquinoline 365



317 **364** **365**

Following general procedure 12, the *title compound* was obtained from 2-iodo-6-methoxy-5-nitroquinoline **317** (4.50 g, 13.6 mmol) and alkyne **364** (5.68 g, 20.4 mmol) as a colourless solid (5.44 g, 83%), mp 146-147 °C (from ethanol); (Found: MH^+, 481.1602. $C_{25}H_{24}N_2O_8$ + H requires 481.1610); ν_{max} ($CHCl_3$)/cm^{-1} 1627 (C=C), 1596 (C=C), 1494 (C=C), 1461 (C=C), 1358 (N=O), 1107 (C-O), 1097 (C-O); δ_H (400 MHz; $CDCl_3$) 8.23 (1 H, d, J = 9.4 Hz, ArH), 8.02 (1 H, d, J = 8.8 Hz, ArH), 7.60 (1 H, d, J = 8.8 Hz, ArH), 7.59 (1 H, d, J = 9.6 Hz, ArH), 7.35 (1 H, d, J = 8.7 Hz, ArH), 6.77 (1 H, d, J = 8.7 Hz, ArH), 5.93 (1 H, s, CH), 5.07 (2 H, s, CH_2), 4.22 - 4.18 (2 H, m, CH_2), 4.08 (3 H, s, OMe), 4.03 - 3.97 (2 H, m, CH_2), 3.90 (3 H, s, OMe), 3.87 (3 H, s, OMe), 2.27 - 2.15 (1 H, m, CH), 1.42 - 1.38 (1 H, m, CH); δ_C (100 MHz; $CDCl_3$) 154.0 (C), 149.8 (C), 149.0 (C), 142.2 (C), 142.1 (C), 141.8 (C), 134.0 (CH), 129.4 (CH), 126.7 (CH), 126.0 (C), 121.7 (CH), 120.4 (C), 116.8 (CH), 108.5 (CH), 97.6 (CH), 86.8 (C), 86.0 (C), 67.6 (CH_2), 61.6 (CH_2), 61.1 (Me), 57.2 (Me), 56.1 (Me), 25.8 (CH_2); *m/z* (ESI) 503 (MNa^+, 20%), 481 (MH^+, 100).

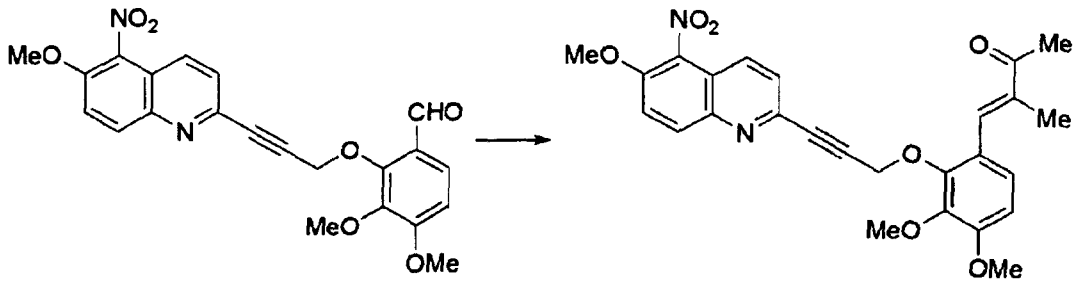
2-(3-(6-Methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)-3,4-dimethoxybenzaldehyde



365

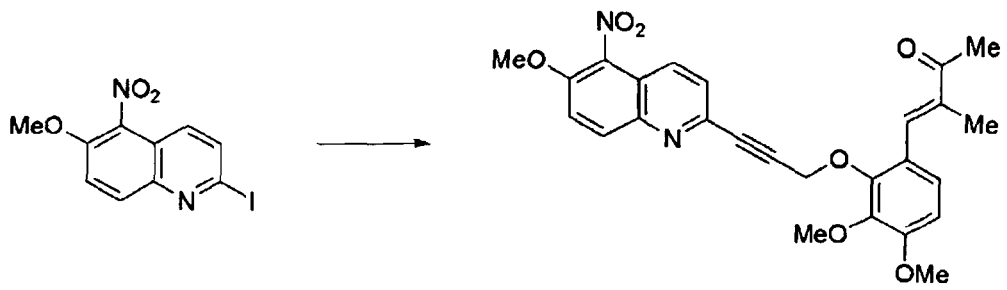
A solution of the acetal **365** (11.0 g, 22.9 mmol) in acetic acid (300 mL) and water (35 mL) was heated to 50 °C for 2 h. The reaction mixture was allowed to cool to room temperature, poured into saturated sodium hydrogen carbonate solution (3000 mL) and extracted with ethyl acetate (5 × 1000 mL). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (1000 mL) and water (1000 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a brown solid (9.67 g, 100%), which was used without further purification, mp 146-147 °C (from ethanol); (Found: MH^+, 423.1189. $C_{22}H_{18}N_2O_7$ + H requires 423.1192); ν_{max} ($CHCl_3$)/cm^{-1} 1679 (C=O), 1627 (C=C), 1592 (C=C), 1495 (C=C), 1460 (C=C), 1357 (N=O), 1093 (C-O); δ_H (400 MHz; $CDCl_3$) 10.4 (1 H, s, CHO), 8.21 (1 H, d, J = 9.5 Hz, ArH), 8.02 (1 H, d, J = 8.8 Hz, ArH), 7.68 (1 H, d, J = 8.8 Hz, ArH), 7.59 (1 H, d, J = 9.5 Hz, ArH), 7.48 (1 H, d, J = 8.8 Hz, ArH), 6.84 (1 H, d, J = 8.8 Hz, ArH), 5.21 (2 H, s, CH_2), 4.08 (3 H, s, OMe), 3.96 (3 H, s, OMe), 3.95 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 189.0 (C), 159.1 (C), 154.2 (C), 149.9 (C), 142.1 (C), 141.9 (C), 141.6 (C), 134.0 (CH), 129.7 (CH), 126.4 (CH), 124.5 (C), 123.9 (CH), 120.5 (C), 116.9 (CH), 108.5 (CH), 87.4 (C≡C), 85.3 (C≡C), 62.1 (CH_2), 61.2 (OMe), 57.2 (OMe), 56.3 (OMe); *m/z* (ESI) 445 (MNa^+, 49%), 423 (MH^+, 100).

4-(2-(3-(6-Methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)-3,4-dimethoxyphenyl)-3-methylbut-3-en-2-one 366



366

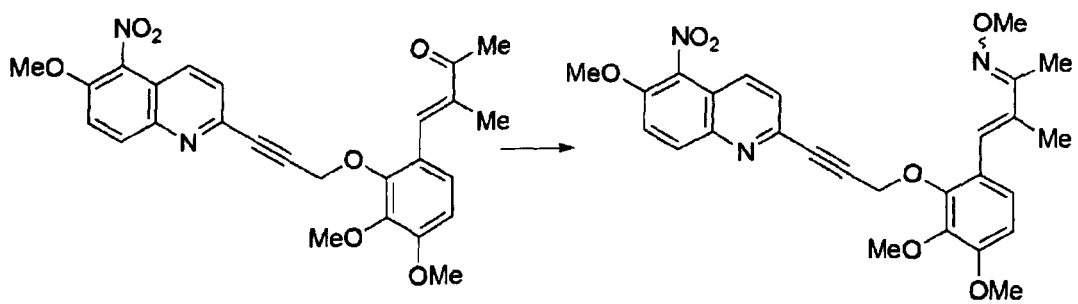
a) Following general procedure 7, the *title compound* was obtained from diethyl 1-methyl-2-oxopropylphosphonate[133] **319** (0.368 g, 1.77 mmol) and the aldehyde (0.500 g, 1.18 mmol) as a colourless solid (0.542 g, 96%), mp 118-120 °C (from ethanol); (Found: MH^+, 477.1669. $C_{26}H_{24}N_2O_7$ + H requires 477.1662); ν_{max} ($CHCl_3$)/cm^{-1} 1659 (C=O), 1627 (C=C), 1597 (C=C), 1494 (C=C), 1455 (C=C), 1357 (N=O), 1099 (C-O); δ_H (400 MHz; $CDCl_3$) 8.20 (1 H, d, J = 9.5 Hz, ArH), 8.02 (1 H, d, J = 8.8 Hz, ArH), 7.92 (1 H, s, C=CH), 7.60 (1 H, d, J = 9.5 Hz, ArH), 7.46 (1 H, d, J = 8.8 Hz, ArH), 7.19 (1 H, d, J = 8.7 Hz, ArH), 6.79 (1 H, d, J = 8.7 Hz, ArH), 5.09 (2 H, s, CH_2), 4.09 (3 H, s, OMe), 3.94 (3 H, s, OMe), 3.93 (3 H, s, OMe), 2.49 (3 H, s, Me), 1.98 (3 H, d, J = 1.3 Hz, Me); δ_C (100 MHz; $CDCl_3$) 200.5 (C), 154.3 (C), 150.5 (C), 149.9 (C), 142.2 (C), 141.7 (C), 136.9 (C), 135.4 (CH), 134.0 (CH), 129.5 (CH), 126.3 (CH), 125.1 (CH), 123.7 (C), 120.4 (C), 117.0 (CH), 107.9 (CH), 86.4 (C), 86.2 (C), 61.6 (CH_2), 61.1 (OMe), 57.2 (OMe), 56.1 (OMe), 25.9 (Me), 13.0 (Me); *m/z* (ESI) 499 (MNa^+, 41%), 477 (MH^+, 100).



317 366

b) Following general procedure 12, the title compound was obtained from 2-iodo-6-methoxy-5-nitroquinoline **317** (0.050 g, 0.151 mmol) and alkyne **349** (0.062 g, 0.227 mmol) as a colourless solid (0.072 g, 100%); data as above.

(3*E*)-4-(3,4-dimethoxy-2-(3-(6-methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)phenyl)-3-methylbut-3-en-2-one *O*-methyl oxime 316

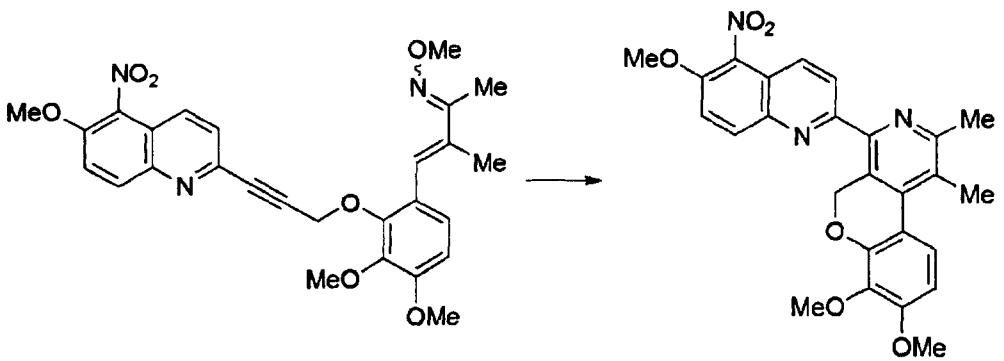


366 316

Following general procedure 9, the *title compound* was obtained from ketone **366** (1.50 g, 3.15 mmol), methoxylamine hydrochloride (0.329 g, 3.94 mmol) and sodium acetate trihydrate (0.450 g, 3.31 mmol) as a pale yellow solid (1.56 g, 98%), mp 98-100 °C (from dichloromethane-hexane); (Found: C, 63.98; H, 5.37; N, 8.15. $C_{27}H_{27}N_3O_7$ requires C, 64.15; H, 5.38; N, 8.31%); (Found: MH^+, 506.1912. $C_{27}H_{27}N_3O_7$ + H requires 506.1922); ν_{max} ($CHCl_3$)/cm^{-1} 1628 (C=C), 1596 (C=C), 1532 (C=C), 1495 (C=C), 1463 (C=C), 1357 (N=O), 1096 (C-O), 1056 (C-O); δ_H (400 MHz; $CDCl_3$) 8.21 (1 H, d, J = 9.6 Hz, ArH), 8.00 (1 H, d, J = 8.8 Hz, ArH), 7.58 (1 H, d, J = 9.6 Hz, ArH), 7.49 (1 H, d, J = 8.8 Hz, ArH), 7.10 (1 H, s, C=CH), 7.04 (1 H,

d, J = 8.8 Hz, ArH), 6.74 (1 H, d, J = 8.8 Hz, ArH), 5.01 (2 H, s, CH_2), 4.08 (3 H, s, OMe), 3.95 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.90 (3 H, s, OMe), 2.10 (3 H, s, Me), 2.01 (3 H, s, Me); δ_C (100 MHz, $CDCl_3$) 157.1 (C), 153.0 (C), 150.0 (C), 149.8 (C), 142.3 (C), 142.1 (C), 142.0 (C), 134.4 (C), 134.0 (CH), 129.4 (CH), 126.6 (CH), 125.9 (CH), 125.1 (CH), 120.3 (C), 116.8 (CH), 107.8 (CH), 86.7 (C≡C), 86.0 (C≡C), 61.7 (OMe), 61.3 (CH_2), 61.1 (OMe), 57.2 (OMe), 56.1 (OMe), 14.4 (Me), 10.9 (Me); *m/z* (ESI) 528 (MNa^+, 100%), 506 (MH^+, 61).

7,8-Dimethoxy-4-(6-methoxy-5-nitroquinolin-2-yl)-1,2-dimethyl-5*H*-chromeno[3,4-c]pyridine 367

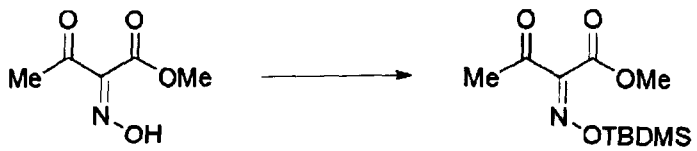


316 **367**

Following general procedure 11, the *title compound* was obtained from *O*-methyl oxime **316** (1.00 g, 1.98 mmol) after 18 h at 140 °C as a pale yellow solid (0.637 g, 68%), mp 211-212 °C (from dichloromethane-hexane); (Found: MH^+, 474.1662. $C_{26}H_{23}N_3O_6$ + H requires 474.1660); ν_{max} ($CHCl_3$)/cm^{-1} 1629 (C=C), 1601 (C=C), 1572 (C=C), 1551 (C=C), 1531 (C=C), 1498 (C=C), 1357 (N=O), 1103 (C-O), 1080 (C-O); δ_H (400 MHz; $CDCl_3$) 8.54 (1 H, d, J = 9.0 Hz, ArH), 8.23 (1 H, d, J = 9.4 Hz, ArH), 8.19 (1 H, d, J = 9.0 Hz, ArH), 7.58 (1 H, d, J = 9.4 Hz, ArH), 7.44 (1 H, d, J = 8.8 Hz, ArH), 6.73 (1 H, d, J = 8.8 Hz, ArH), 5.61 (2 H, s, CH_2), 4.10 (3 H, s, OMe), 3.97 (3 H, s, OMe), 3.94 (3 H, s, OMe), 2.70 (3 H, s, Me), 2.60 (3 H, s, Me); δ_C (100

MHz; $CDCl_3$) 157.2 (C), 156.9 (C), 153.8 (C), 151.3 (C), 149.3 (C), 147.9 (C), 141.1 (C), 138.5 (C), 138.0 (C), 134.8 (C), 134.0 (CH), 129.5 (CH), 127.4 (C), 126.7 (C), 124.1 (CH), 123.8 (CH), 120.3 (C), 117.3 (C), 116.0 (CH), 104.9 (CH), 67.5 (CH_2), 61.3 (OMe), 57.1 (OMe), 56.0 (OMe), 24.0 (Me), 18.0 (Me); *m/z* (ESI) 474 (MH^+, 100%), 151 (16), 130 (20).

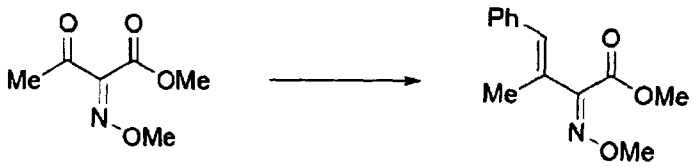
Methyl oximinoacetoacetate-*O*-*tert*-butyldimethylsilyl ether 370



233 **370**

To a solution of methyl oximinoacetoacetate (3.63 g, 25.0 mmol) in dichloromethane (30 mL) at 0 °C was added diisopropylethylamine (5.62 mL, 32.5 mmol) and *tert*-butlydimethylsilyl trifluoromethanesulfonate (7.18 mL, 31.3 mmol) dropwise. Stirring was continued at 0 °C for 2 h. The solvent was removed *in vacuo*, and the resulting residue diluted with *n*-pentane (20 mL). The suspension was stirred at 0 °C for 1 h. The solid was filtered off, and the filtrate concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with dichloromethane, to afford the *title compound* as a colourless oil (5.75 g, 89%); (Found: MNa^+, 282.1136. $C_{11}H_{21}NO_4Si$ + Na requires 282.1138); ν_{max} ($CHCl_3$)/cm^{-1} 1747 (C=O), 1693 (C=O); δ_H (400 MHz; $CDCl_3$) 3.85 (3 H, s, OMe), 2.39 (3 H, s, Me), 0.93 (9 H, s, CMe_3), 0.25 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 193.4 (C), 162.0 (C), 155.2 (C), 52.3 (OMe), 25.6 ($C\underline{Me}_3$), 25.3 (Me), 18.1 ($\underline{C}Me_3$), -5.5 ($SiMe_2$); m/z (ESI) 541 (19%), 374 (19), 282 (MNa^+, 100), 260 (MH^+, 7%).

Methyl 2-methoxyimino-3-methyl-4-phenylbut-3-enoate[167] 371



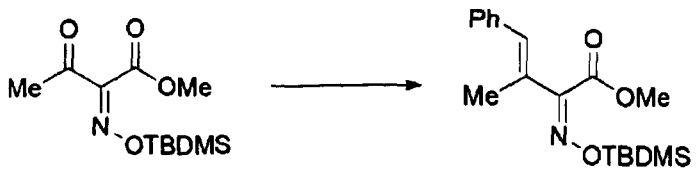
235 **371**

a) To a stirred suspension of sodium hydride (0.054 g, 1.35 mmol) in DME (3 mL) at 0 °C was added benzyltriphenylphosphonium chloride **369** (0.506 g, 1.30 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 30 min, and cooled back to 0 °C. Methyl methoxyiminoacetoacetate **235** (0.145 g, 1.00 mmol) was added and the reaction mixture stirred at room temperature for 17 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound as a colourless oil (0.187 g, 81%); ν_{max} ($CHCl_3$)/cm^{-1} 1738 (C=O), 1600 (C=C), 1490 (C=C), 1460 (C=C), 1082 (C-O), 1045 (C-O); δ_H (400 MHz; $CDCl_3$) 7.39-7.28 (5 H, m, ArH), 6.56 (1 H, s, CH), 3.99 (3 H, s, OMe), 3.94 (3 H, s, OMe), 2.12 (3 H, d, J = 1.3 Hz, Me); δ_C (100 MHz; $CDCl_3$) 164.7 (C), 154.6 (C), 136.1 (C), 134.5 (CH), 129.9 (CH), 129.4 (CH), 128.3 (CH), 127.7 (CH), 62.9 (Me), 52.3 (Me), 13.5 (Me).

b) To a stirred solution of benzyltriphenylphosphonium chloride (0.583 g, 1.50 mmol) in DME (3 mL) at 0 °C was added potassium *tert*-butoxide (0.174 g, 1.55 mmol) portionwise. The reaction mixture was allowed to warm to room temperature, stirred for 30 min, then cooled back to 0 °C. Methyl methoxyiminoacetoacetate **235** (0.145 g, 1.00 mmol) was added and the reaction mixture stirred at room temperature for 17 h. The reaction was quenched with saturated ammonium chloride (10 mL), and extracted

with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound as a colourless oil (0.197 g, 85%); data as above.

Methyl 2-*tert*-butyldimethylsiloxyimino-3-methyl-4-phenylbut-3-enoate 372



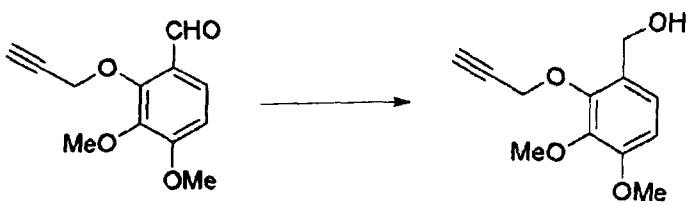
370 **372**

a) To a stirred suspension of sodium hydride (0.054 g, 1.35 mmol) in DME (3 mL) at 0 °C was added benzyltriphenylphosphonium chloride (0.506 g, 1.30 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 30 min, then cooled back to 0 °C. Methyl oximinoacetoacetate *tert*-butyldimethylsilyl ether **370** (0.259 g, 1.00 mmol) was added and the reaction mixture stirred at room temperature for 17 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9), to afford the *title compound* as a colourless oil (0.220 g, 66%); (Found: MH^+, 334.1828. $C_{18}H_{26}NO_3Si$ + H requires 334.1833); ν_{max} ($CHCl_3$)/cm^{-1} 1739 (C=O), 1601 (C=C), 1490 (C=C), 1462 (C=C), 1079 (C-O); δ_H (400 MHz; $CDCl_3$) 7.39 - 7.26 (5 H, m, ArH), 6.59 (1 H, s, CH), 3.91 (3 H, s, OMe), 2.12 (3 H, d, J = 1.3 Hz, Me), 0.96 (9 H, s, CMe_3), 0.22 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 165.1 (C), 159.4 (C), 136.2 (C), 134.4 (CH), 130.2 (C), 129.4 (CH), 128.3 (CH), 127.7 (CH), 52.0 (OMe), 25.9

($C\underline{Me}_3$), 18.1 ($\underline{C}Me_3$), 13.5 (Me), -5.4 (Me); *m/z* (ESI) 356 (MNa^+, 24%), 334 (MH^+, 100), 279 (11).

b) To a stirred solution of benzyltriphenylphosphonium chloride (0.506 g, 1.30 mmol) in DME (3 mL) at 0 °C was added potassium *tert*-butoxide (0.152 g, 1.35 mmol) portionwise. The reaction mixture was allowed to warm to room temperature, stirred for 30 min, then cooled back to 0 °C. Methyl methoxyiminoacetoacetate **370** (0.145 g, 1.00 mmol) was added and the reaction mixture stirred at room temperature for 17 h. The reaction was quenched with saturated ammonium chloride (10 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound as a colourless oil (0.270 g, 81%); data as above.

1-(Hydroxymethyl)-3,4-dimethoxy-2-(prop-2-ynyloxy)benzene 373

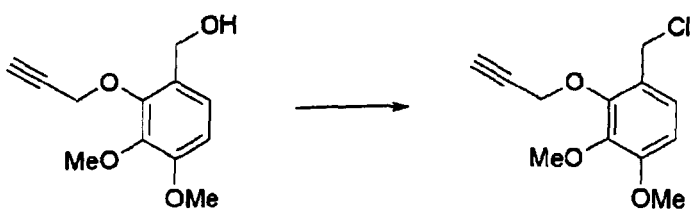


318 **373**

To a solution of 3,4-dimethoxy-2-(prop-2-ynyloxy)benzaldehyde **318** (1.50 g, 6.81 mmol) in methanol (150 mL) at 0 °C was added sodium borohydride (0.386 g, 10.2 mmol) portionwise. Stirring was continued at 0 °C for 1 h. The solvent was removed *in vacuo* and the residue partitioned between water (50 mL) and dichloromethane (3 × 50 mL). The combined organics were washed with water (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a pale yellow solid (1.51 g,

100%), mp 53-54 °C (from ethyl acetate-hexane); (Found: C, 64.45; H, 6.29. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%); (Found: MNa^+, 245.0784. $C_{12}H_{14}O_4$ + Na requires 245.0784); ν_{max} ($CHCl_3$)/cm^{-1} 3606 (O-H), 3306 (alkyne C-H), 2123 (C≡C), 1602 (C=C), 1496 (C=C), 1461 (C=C), 1308 (C-O), 1278 (C-O), 1097 (C-O); δ_H (400 MHz; $CDCl_3$) 7.03 (1 H, d, *J* = 8.5 Hz, ArH), 6.69 (1 H, d, *J* = 8.5 Hz, ArH), 4.87 (2 H, d, *J* = 2.4 Hz, C≡CCH_2), 4.67 (2 H, d, *J* = 6.0 Hz, ArCH_2), 3.87 (3 H, s, OMe), 3.86 (3 H, s, OMe), 2.51 (1 H, t, *J* = 2.4 Hz, C≡CH), 2.17 (1 H, t, *J* = 6.2 Hz, OH); δ_C (100 MHz; $CDCl_3$) 153.6 (C), 149.5 (C), 141.9 (C), 127.7 (C), 123.7 (CH), 107.8 (CH), 79.4 (C≡CH), 75.6 (C≡CH), 61.4 (CH_2), 60.9 (Me), 60.6 (CH_2), 56.0 (Me); *m/z* (ESI) 245 (MNa^+, 41), 205 (M-OH, 100), 174 (14).

1-(Chloromethyl)-3,4-dimethoxy-2-(prop-2-ynyloxy)benzene 374

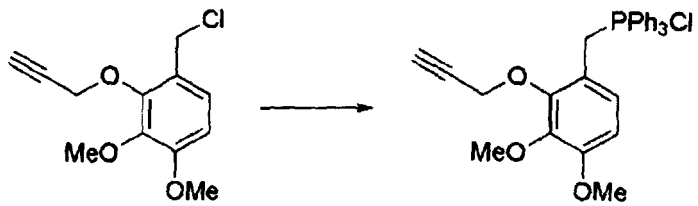


373 **374**

To a solution of 1-(hydroxymethyl)-3,4-dimethoxy-2-(prop-2-ynyloxy)benzene **373** (1.01 g, 4.57 mmol) and pyridine (0.55 mL, 6.86 mmol) in dichloromethane (15 mL) was added thionyl chloride (0.67 g, 9.14 mmol). The reaction mixture was stirred at room temperature for 3 h, then poured onto water (20 mL). The aqueous layer was extracted with dichloromethane (2 × 25 mL). The combined organics were washed with hydrochloric acid (2 M; 2 × 25 mL) and saturated brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a brown solid (1.01 g, 86%), mp 36-38 °C (from ethanol); (Found: $[M-Cl]^+$, 205.0861. $C_{12}H_{13}ClO_3$ - Cl 205.0859); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C-H), 2125 (C≡C), 1601 (C=C), 1496

(C=C), 1462 (C=C), 1096 (C-O); δ_H (400 MHz; $CDCl_3$) 7.09 (1 H, d, J = 8.6 Hz, ArH), 6.71 (1 H, d, J = 8.6 Hz, ArH), 4.85 (2 H, d, J = 2.4 Hz, C≡CCH_2), 4.68 (2 H, s, ArCH_2), 3.88 (3 H, s, OMe), 3.86 (3 H, s, OMe), 2.51 (1 H, t, J = 2.4 Hz, C≡CH); δ_C (100 MHz; $CDCl_3$) 154.2 (C), 149.7 (C), 142.2 (C), 125.0 (CH), 124.5 (C), 108.1 (CH), 79.1 (C≡CH), 75.5 (C≡CH), 60.9 (Me), 60.8 (CH_2), 56.0 (Me), 41.8 (CH_2); *m/z* (ESI) 259 (16%), 205 ($[M-Cl]^+$, 100), 174 (12).

1-(Triphenylphosphinomethyl)-3,4-dimethoxy-2-(prop-2-ynyloxy)benzene 375

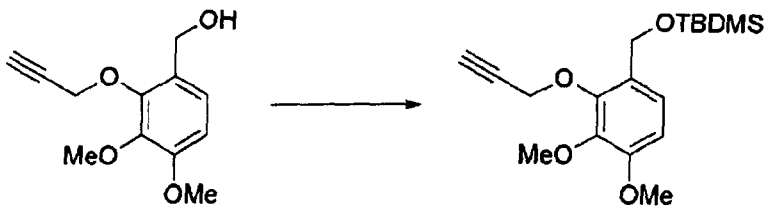


374 **375**

To a solution of 1-(chloromethyl)-3,4-dimethoxy-2-(prop-2-ynyloxy)benzene **374** (0.478 g, 1.86 mmol) in toluene (2 mL) was added triphenylphosphine (0.488 g, 1.86 mmol) in toluene (3 mL). The reaction mixture was heated at 60 °C for 18 h. The solid was filtered off, washed with ether and dried *in vacuo* at 40 °C to afford the *title compound* as a colourless solid (0.776 g, 83%), mp 208-209 °C (from toluene); (Found: $[M-Cl]^+$, 467.1772. $C_{30}H_{28}ClO_3P$ - Cl requires 467.1771); ν_{max} ($CHCl_3$)/cm^{-1} 3305 (alkyne C-H), 1601 (C=C), 1495 (C=C), 1462 (C=C), 1110 (C-O), 1096 (C-O), 1041 (C-O); δ_H (400 MHz; $CDCl_3$) 7.78-7.60 (15 H, m, ArH), 7.21 (1 H, dd, J = 2.9 and 8.7 Hz, H-5), 6.57 (1 H, d, J = 8.7 Hz, H-4), 5.35 (2 H, d, J = 13.5 Hz, ArCH_2), 4.39 (2 H, d, J = 2.4 Hz, C≡CCH_2), 3.79 (3 H, s, OMe), 3.57 (3 H, s, OMe), 2.61 (1 H, t, J = 2.4 Hz, C≡CH); δ_C (100 MHz; $CDCl_3$) 134.8 (CH), 134.7 (C), 134.4 (CH), 134.3 (CH), 130.1 (CH), 130.0 (CH), 127.2 (CH), 127.1 (C), 118.7 (C), 117.9 (C), 108.4

(CH), 79.0 (C≡CH), 76.3 (C≡CH), 60.6 (Me), 60.4 (CH_2), 56.0 (Me); *m/z* (ESI) 467 ($[M-Cl]^+$, 100%).

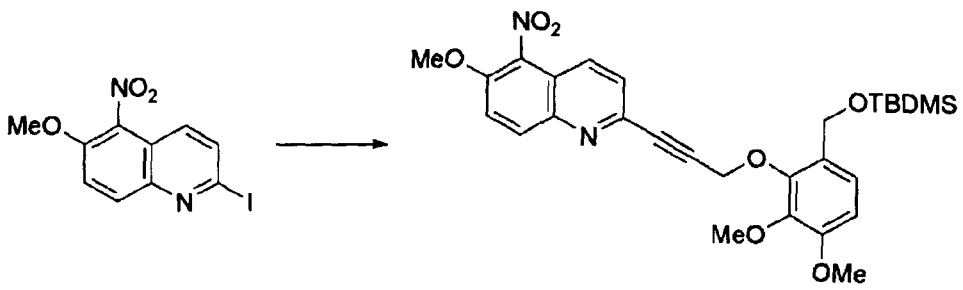
1-(*tert*-Butyldimethylsilanyloxymethyl)-2-(prop-2-ynyloxy)-3,4-dimethoxybenzene 378



373 **378**

To a solution of 1-(hydroxymethyl)-3,4-dimethoxy-2-(prop-2-ynyloxy)benzene **373** (0.445 g, 2.00 mmol) and *tert*-butyldimethylchlorosilane (0.377 g, 2.50 mmol) in dichloromethane (2 mL) was added imidazole (0.204 g, 3.00 mmol) in dichloromethane (3 mL). Stirring was continued for 3 h. The crude reaction mixture was purified by flash chromatography on silica gel, eluting with dichloromethane, to afford the *title compound* as a colourless oil (0.588 g, 94%); (Found: MNa^+, 359.1650. $C_{18}H_{28}O_4Si$ + Na requires 359.1649); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C-H), 2124 (C≡C), 1603 (C=C), 1495 (C=C), 1461 (C=C), 1094 (C-O), 1041 (Si-O), 1004 (C-O); δ_H (400 MHz; $CDCl_3$) 7.13 (1 H, d, J = 8.6 Hz, ArH), 6.72 (1 H, d, J = 8.6 Hz, ArH), 4.79 (2 H, s, $ArCH_2$), 4.78 (2 H, d, J = 2.4 Hz, $C{\equiv}CCH_2$), 3.87 (3 H, s, OMe), 3.86 (3 H, s, OMe), 2.47 (1 H, t, J = 2.4 Hz, C≡CH), 0.96 (9 H, s, CMe_3), 0.12 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 152.6 (C), 148.4 (C), 141.8 (C), 128.1 (C), 121.9 (CH), 107.8 (CH), 79.6 (C≡CH), 75.0 (C≡CH), 60.9 (Me), 60.4 (CH_2), 60.3, 56.0 (Me), 26.0 (CMe_3), 18.4 (CMe_3), -5.3 (Me); *m/z* (ESI) 359 (MNa^+, 57%), 205 (M-OTBDMS, 100), 174 (17).

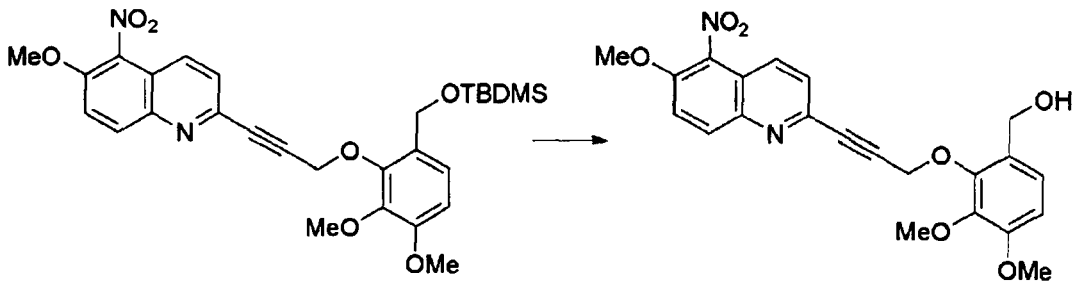
2-{3-[6-(*tert*-Butyldimethylsilanyloxymethyl)-2,3-dimethoxy-phenoxy]-prop-1-ynyl}-6-methoxy-5-nitroquinoline 379



317 **379**

Following general procedure 12, the *title compound* was obtained from 2-iodo-6-methoxy-5-nitroquinoline **317** (0.500 g, 1.51 mmol) and alkyne **378** (0.712 g, 2.27 mmol) as a colourless oil (0.570 g, 70%); (Found: MH^+, 539.2221. $C_{28}H_{34}N_2O_7Si$ + H requires 539.2208); ν_{max} ($CHCl_3$)/cm^{-1} 1628 (C=C), 1595 (C=C), 1550 (C=C), 1494 (C=C), 1461 (C=C), 1358 (N=O), 1094 (C-O), 1080 (C-O), 1033 (Si-O), 992 (C-O); δ_H (400 MHz; $CDCl_3$) 8.21 (1 H, dd, J = 0.6 and 9.4 Hz, ArH), 8.00 (1 H, dd, J = 0.6 and 8.8 Hz, ArH), 7.58 (1 H, d, J = 9.5 Hz, ArH), 7.53 (1 H, d, J = 8.8 Hz, ArH), 7.14 (1 H, d, J = 8.6 Hz, ArH), 6.73 (1 H, d, J = 8.6 Hz, ArH), 5.06 (2 H, s, CH_2), 4.84 (2 H, s, CH_2), 4.07 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.86 (3 H, s, OMe), 0.92 (9 H, s, CMe_3), 0.09 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 152.7 (C), 149.8 (C), 148.5 (C), 142.1 (C), 141.9 (C), 134.5 (C), 134.0 (CH), 129.4 (CH), 128.1 (C), 126.6 (CH), 122.1 (CH), 120.3 (C), 116.9 (CH), 108.0 (CH), 86.9 (C≡C), 85.8 (C≡C), 61.0 (OMe), 60.9 (CH_2), 60.4 (CH_2), 57.2 (OMe), 56.0 (OMe), 26.0 ($C\underline{Me}_3$), 18.4 ($\underline{C}Me_3$), -5.3 ($SiMe_2$); *m/z* (ESI) 561 (MNa^+, 25%), 539 (MH^+, 32), 407 (100).

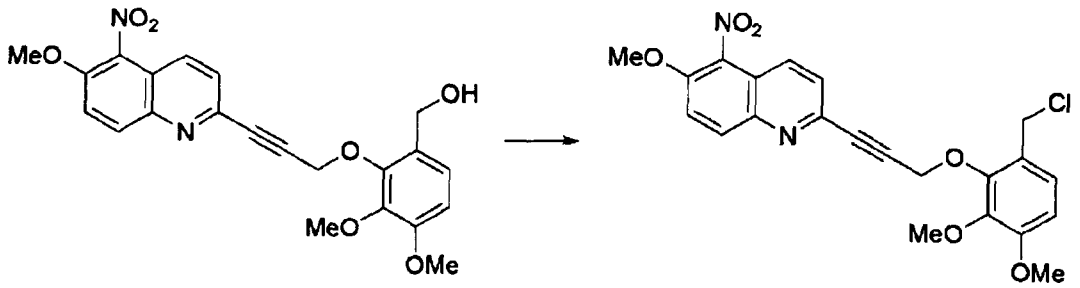
(2-(3-(6-Methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)-3,4-dimethoxyphenyl)methanol



379

To a solution of quinoline **379** (0.500 g, 0.928 mmol) in methanol (15 mL) was added Dowex-50W^{TM} acidic resin (0.150 g). The reaction mixture was stirred at room temperature for 5 h. The solvent was removed *in vacuo*, and the residue diluted with chloroform (150 mL) and filtered. The filtrate was concentrated *in vacuo* to afford the *title compound* as a colourless solid (0.373 g, 95%), mp 161-162 °C from (dichloromethane-hexane); (Found: MNa^+, 447.1165. $C_{22}H_{20}N_2O_7$ + Na requires 447.1174); ν_{max} ($CHCl_3$)/cm^{-1} 1628 (C=C), 1596 (C=C), 1495 (C=C), 1536 (C=C), 1496 (C=C), 1459 (C=C), 1356 (N=O), 1096 (C-O), 1006 (C-O); δ_H (400 MHz; $CDCl_3$) 8.19 (1 H, d, J = 9.5 ArH), 8.00 (1 H, d, J = 8.8 Hz, ArH), 7.57 (1 H, d, J = 9.5 Hz, ArH), 7.50 (1 H, d, J = 8.8 Hz, ArH), 7.19 (1 H, d, J = 8.6 Hz, ArH), 6.75 (1 H, d, J = 8.6 Hz, ArH), 5.12 (2 H, s, CH_2), 4.83 (2 H, s, CH_2), 4.08 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.87 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 153.2 (C), 60.9 (CH_2), 149.9 (C), 60.2 (CH_2), 142.0 (C), 57.2 (OMe), 141.8 (C), 56.1 (OMe), 141.7 (C), 133.7 (CH), 129.8 (CH), 128.8 (C), 126.0 (CH), 123.8 (CH), 120.4 (C), 117.0 (CH), 108.5 (CH), 87.0 (C≡C), 86.6 (C≡C), 61.0 (OMe); *m/z* (ESI) 447 (MNa^+, 35%), 425 (MH^+, 23), 407 (100).

2-(3-(6-(Chloromethyl)-2,3-dimethoxyphenoxy)prop-1-ynyl)-6-methoxy-5-nitroquinoline 380



380

To a solution of the benzyl alcohol (0.210 g, 0.495 mmol) in dichloromethane (5 mL) was added pyridine (0.060 mL, 0.743 mmol) and thionyl chloride (0.072 mL, 0.990 mmol). The reaction mixture was stirred at room temperature for 3 h, poured into water (15 mL) and extracted into dichloromethane (2 × 15 mL). The combined organics were washed with hydrochloric acid (2 M; 2 × 15 mL) and saturated brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a colourless solid (0.219 g, 100%); Found: MH^+, 443.1001. $C_{22}H_{19}ClN_2O_6$ + H requires 443.1004); ν_{max} ($CHCl_3$)/cm^{-1} 1627 (C=C), 1603 (C=C), 1532 (C=C), 1500 (C=C), 1463 (C=C), 1366 (N=O); δ_H (400 MHz; $CDCl_3$) 8.22 (1 H, d, J = 9.2 Hz, ArH), 8.02 (1 H, d, J = 8.8 Hz, ArH), 7.59 (1 H, d, J = 9.2 Hz, ArH), 7.57 (1 H, d, J = 8.8 Hz, ArH), 7.12 (1 H, d, J = 8.8 Hz, ArH), 6.73 (1 H, d, J = 8.8 Hz, ArH), 5.16 (2 H, s, CH_2), 4.75 (2 H, s, CH_2), 4.07 (3 H, s, OMe), 3.93 (3 H, s, OMe), 3.87 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 153.2 (C), 148.8 (C), 148.7 (C), 141.2 (C), 141.0 (C), 140.9 (C), 133.0 (CH), 128.5 (CH), 125.6 (CH), 124.1 (CH), 123.2 (C), 119.3 (C), 115.8 (CH), 107.2 (CH), 85.4 (C≡C), 85.1 (C≡C), 60.3 (CH_2), 60.0 (OMe), 56.2 (OMe), 55.0 (OMe), 40.7 (CH_2); *m/z* (ESI) 522 (100%), 443 (MH^+, 51), 366 (27), 338 (25), 301 (37).

2-Ketobutanoic acid methyl ester[173]

To a solution of 2-ketobutanoic acid (3.06 g, 30.0 mmol) in methanol (12 mL) and acetone dimethylacetal (48 mL) was added chlorotrimethylsilane (0.38 mL, 3.00 mmol). The reaction mixture was stirred at room temperature for 19 h and concentrated *in vacuo* to afford the title compound as a colourless oil (2.51 g, 72%); ν_{max} ($CHCl_3$)/cm^{-1} 1732 (C=O); δ_H (400 MHz; $CDCl_3$) 3.81 (3 H, s, OMe), 2.82 (2 H, q, J = 7.2 Hz, CH_2), 1.07 (3 H, t, J = 7.2 Hz, Me); δ_C (100 MHz; $CDCl_3$) 194.7 (C), 161.5 (C), 52.8 (OMe), 32.8 (CH_2), 6.9 (Me).

α-Bromo-2-ketobutanoic acid methyl ester[171] **382**

382

Bromine (0.88 mL, 17.2 mmol) was added dropwise over 30 min to 2-ketobutanoic acid methyl ester (2.00 g, 17.2 mmol) at 0 °C. Stirring was continued at 0 °C for 20 min. The reaction was then quenched by the careful addition of saturated sodium hydrogen carbonate (20 mL). The aqueous layer was extracted with ether (2 × 35 mL), and the combined organics washed with saturated sodium hydrogen carbonate (2 × 35 mL), water (35 mL) and saturated brine (35 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a colourless oil (2.12 g, 63%); ν_{max} ($CHCl_3$)/cm^{-1} 1784 (C=O), 1733 (C=O); δ_H (400 MHz; $CDCl_3$) 5.17 (1 H, q, J = 6.8 Hz, CH), 3.93 (3 H, s, OMe), 1.81 (3 H, d, J = 6.8 Hz, Me); δ_C (100 MHz; $CDCl_3$)

162.0 (C), 150.1 (C), 64.0 (OMe), 52.8 (OMe), 33.2 (CH), 21.9 (Me); δ_C (100 MHz; $CDCl_3$) 186.9 (C), 161.0 (C), 53.5 (OMe), 42.3 (CH), 18.5 (Me).

Methyl 3-bromo-2-(methoxyimino)propanoate[172] 383

381 **383**

To a solution of methyl bromopyruvate **381** (3.62 g, 20.0 mmol) in methanol (60 mL) was added methoxylamine hydrochloride (2.51 g, 30.0 mmol) in one portion. The reaction mixture was stirred at room temperature for 22 h and the solvent removed *in vacuo*. The residue was partitioned between water (50 mL) and ether (3 × 75 mL). The combined organics were washed with water (2 × 75 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a colourless oil (3.76 g, 90%), which was used without further purification; ν_{max} ($CHCl_3$)/cm^{-1} 1736 (C=O), 1599 (C=N); δ_H (400 MHz; $CDCl_3$) 4.37 (2 H, s, CH_2), 4.18 (3 H, s, OMe), 3.92 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 162.3 (C), 146.9 (C), 64.3 (OMe), 53.2 (OMe), 30.9 (CH_2).

Methyl 3-bromo-2-(methoxyimino)butanoate 384

382 **384**

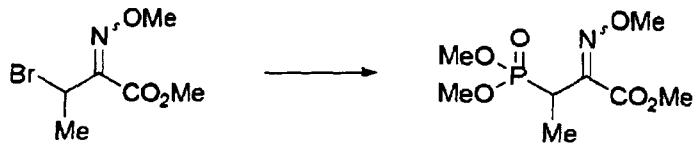
To a solution of methyl 3-bromo-2-oxobutanoate **382** (1.00 g, 5.13 mmol) in methanol (20 mL) was added methoxylamine hydrochloride (2.14 g, 25.7 mmol) and magnesium sulfate (2.00 g). The reaction mixture was stirred at room temperature for

16 h, filtered and concentrated *in vacuo*. The residue was partitioned between water (75 mL) and ethyl acetate (3 × 75 mL). The combined organics were washed with water (3 × 75 mL) and saturated brine (75 mL), dried over $MgSO_4$ and concentrated in vacuo to afford the *title compound* as a colourless oil (0.995 g, 87%), which was used without further purification; (Found: MH^+, 254.0786. $C_8H_{16}NO_5P$ + H requires 254.0788); ν_{max} ($CHCl_3$)/cm^{-1} 1736 (C=O), 1586 (C=N); δ_H (360 MHz; $CDCl_3$) 5.39 (1 H, q, J = 7.1 Hz, CH), 4.12 (3 H, s, OMe), 3.88 (3 H, s, OMe), 1.93 (3 H, d, J = 7.1 Hz, Me); δ_C (100 MHz; $CDCl_3$) 162.0 (C), 150.1 (C), 64.0 (OMe), 52.8 (OMe), 33.2 (CH), 21.9 (Me); *m/z* (ESI) 276 (MNa^+, 100%), 254 (MH^+, 8).

Methyl 3-(dimethoxyphosphino)-2-(methoxyimino)propanoate[172] 385

A solution of (*E*)-methyl 3-bromo-2-(methoxyimino)propanoate **383** (3.76 g, 17.9 mmol) in trimethyl phosphite (2.96 g, 25.0 mmol) was heated under reflux for 48 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (3:1) to afford the title compound as a colourless oil (2.54 g, 59%); ν_{max} ($CHCl_3$)/cm^{-1} 1736 (C=O), 1242 (P=O), 1031 (P-O); δ_H (400 MHz; $CDCl_3$) 4.06 (3 H, s, OMe), 3.82 (3 H, s, OMe), 7.72 (3 H, d, J = 4.8 Hz, POMe), 3.68 (3 H, d, J = 4.8 Hz, POMe), 3.27 (2 H, d, J = 23.6 Hz, CH_2); δ_C (100 MHz; $CDCl_3$) 163.0 (d, $^3J_{C\text{-}P}$ = 8.0 Hz, C), 143.4 (d, $^2J_{C\text{-}P}$ = 12.0 Hz, C), 63.6 (OMe), 53.0 (OMe, d, $^2J_{C\text{-}P}$ = 6.0 Hz), 52.9 (OMe, d, $^2J_{C\text{-}P}$ = 6.0 Hz), 23.3 (CH_2, d, $^1J_{C\text{-}P}$ = 136.2 Hz).

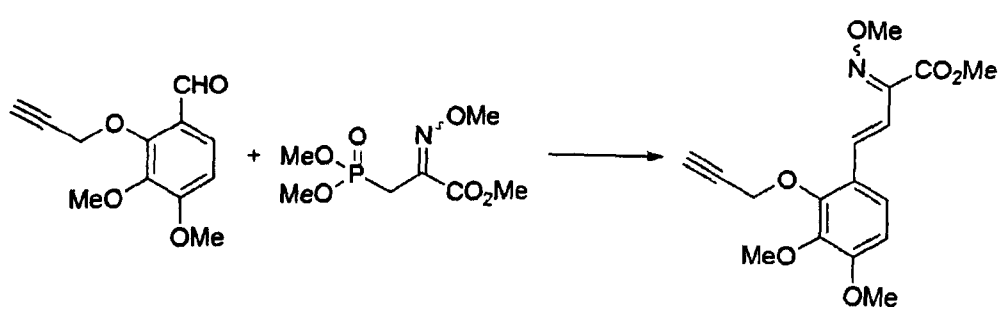
Methyl 3-(dimethoxyphosphoryl)-2-(methoxyimino)butanoate 386



384 **386**

A solution of (*E*)-methyl 3-bromo-2-(methoxyimino)butanoate **384** (0.650 g, 2.90 mmol) in triethylphosphite (0.48 mL, 4.06 mmol) was heated under reflux for 38 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (3:1) to afford the title compound as a colourless oil (0.171 g, 23%); ν_{max} ($CHCl_3$)/cm^{-1} 1733 (C=O), 1256 (P=O), 1093 (P-O); δ_H (400 MHz; $CDCl_3$) 4.05 (3 H, s, OMe), 3.93 (1 H, dq, J = 31.2 and 6.0 Hz, PCH), 3.82 (3 H, s, OMe), 3.72 (3 H, d, J = 6.4 Hz, POMe), 3.69 (3 H, d, J = 6.4 Hz, POMe), 1.45 (3 H, dd, J = 17.5 and 8.5 Hz, Me); δ_C (100 MHz; $CDCl_3$) 163.0 (d, $^3J_{C\text{-}P}$ = 3.0 Hz, C), 148.0 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, C), 63.6 (OMe), 53.4 (d, J = 6.0 Hz, POMe), 52.9 (d, J = 6.0 Hz, POMe), 52.2 (OMe), 30.2 (d, J = 114.1 Hz, CH), 11.9 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, Me).

(3*E*)-methyl 4-(3,4-dimethoxy-2-(prop-2-ynyloxy)phenyl)-2-(methoxyimino)but-3-enoate 387

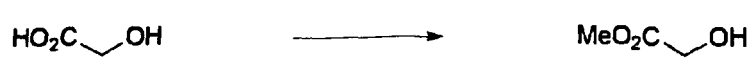


318 **385** **387**

To a solution of (*E*)-methyl 3-(dimethoxyphosphino)-2-(methoxyimino)propanoate **385** (0.957 g, 4.00 mmol) in THF (8 mL) at -78 °C was added *n*-butyllithium (2.5 M in

hexanes; 1.60 mL, 4.00 mmol) dropwise over 20 min. The reaction mixture was stirred at -78 °C for 1 h. A solution of 3,4-dimethoxy-2-(prop-2-ynyloxy)benzaldehyde **318** (0.440 g, 2.00 mmol) in THF (12 mL) was added dropwise over 20 min. The reaction mixture was allowed to warm to room temperature and stirred for 6 h. Saturated ammonium chloride (50 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organics were washed with water (50 mL) and saturated brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9 to 1:4) to afford the *title compound* as a colourless solid (0.331 g, 50%), mp 87-88 °C (from dichloromethane-hexane); (Found: C, 61.25; H, 5.75; N, 4.06. $C_{17}H_{19}NO_6$ requires C, 61.25; H, 5.75; N, 4.20%); (Found: MH^+, 334.1272. $C_{17}H_{19}NO_6$ + H requires 334.1285); ν_{max} ($CHCl_3$)/cm^{-1} 3308 (alkyne C-H), 2126 (C≡C), 1733 (C=O), 1596 (C=C), 1593 (C=C), 1497 (C=C), 1097 (C-O); δ_H (500 MHz; $CDCl_3$) 7.92 (1 H, d, J = 17.0 Hz, C=CH), 7.36 (1 H, d, J = 9.0 Hz, ArH), 7.13 (1 H, d, J = 17.0 Hz, C=CH), 6.73 (1 H, d, J = 9.0 Hz, ArH), 4.78 (2 H, d, J = 2.5 Hz, CH_2), 4.12 (3 H, s, OMe), 3.93 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.93 (3 H, s, OMe), 2.50 (1 H, t, J = 2.5 Hz, C≡CH), 2.18 (3 H, s, Me); 163.8 (C), 154.7 (C), 150.5 (C), 147.9 (C), 142.3 (C), 135.1 (CH), 124.0 (C), 121.5 (CH), 112.7 (CH), 110.0 (C), 108.3 (CH), 78.9 (C≡C), 75.7 (C≡C), 63.5 (OMe), 61.0 (CH_2), 56.1 (OMe), 52.8 (OMe); *m/z* (ESI) 356 (MNa^+, 100%), 334 (MH^+, 34).

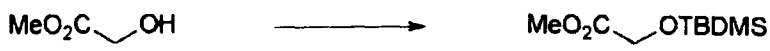
Methyl Glycolate[174]



To a solution of glycolic acid (22.8 g, 300 mmol) in methanol (300 mL) was added boric acid (1.85 g, 30.0 mmol). The reaction mixture was stirred at room temperature

for 15 h then concentrated *in vacuo*. The crude product was purified by distillation (40 °C at 20 mm Hg) to afford the title compound as a colourless oil (15.1 g, 56%); ν_{max} ($CHCl_3$)/cm^{-1} 3547 (O-H), 1746 (C=O); δ_H (500 MHz; $CDCl_3$) 4.12 (2 H, s, CH_2), 3.73 (3 H, s, OMe); δ_C (125 MHz; $CDCl_3$) 173.9 (C), 60.4 (CH_2), 52.2 (Me).

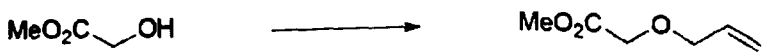
Methyl 2-(*tert*-butyldimethylsilyloxy)acetate[175] 392



392

To a solution of methyl glycolate (0.568 g, 6.31 mmol) in THF (15 mL) was added *tert*-butyldimethylchlorosilane (1.14 g, 7.57 mmol) and imidazole (1.29 g, 18.9 mmol). The reaction mixture was stirred at room temperature for 2 h then partitioned between water (50 mL) and dichloromethane (3 × 50 mL). The combined organics were washed with water (50 mL) and saturated brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound as a colourless oil (0.475 g, 37%); ν_{max} ($CHCl_3$)/cm^{-1} 1757 (C=O); δ_H (400 MHz; $CDCl_3$) 4.24 (2 H, s, CH_2), 3.73 (3 H ,s, OMe), 0.90 (9 H, s, $C\underline{Me}_3$), 0.10 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 172.1 (C), 61.7 (CH_2), 57.7 (OMe), 25.6 ($C\underline{Me}_3$), 14.2 ($\underline{C}Me_3$), -5.5 ($SiMe_2$).

Methyl 2-(allyloxy)acetate[204] 393

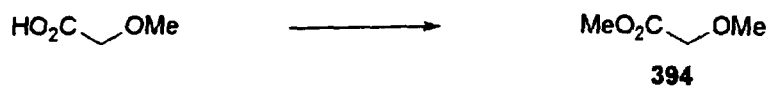


393

Methyl glycolate (5.00 g, 55.5 mmol) was added to a solution of sodium hydride (2.44 g, 61.1 mmol) in DMF (100 mL). The reaction mixture was stirred at room temperature for 19 h and quenched by careful addition of saturated ammonium

chloride (250 mL). The aqueous layer was extracted with ether (4 × 250 mL) and the combined organic extracts washed with water (4 × 250 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound as a colourless oil (2.94 g, 41%); ν_{max} ($CHCl_3$)/cm^{-1} 1750 (C=O), 1602 (C=C); δ_H (400 MHz; $CDCl_3$) 5.96-5.89 (1 H, m, CH_2=C<u>H</u>), 5.30 (1 H, ddt, J = 17.2, 1.6 and 1.5 Hz, C<u>H$_2$</u>=CH), 5.23 (1 H, ddt, J = 10.4, 1.6 and 1.2 Hz, C<u>H$_2$</u>=CH), 4.11 (2 H, m, CHC<u>H$_2$</u>), 4.10 (2 H, s, CH_2), 3.76 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 170.8 (C), 133.7 (CH), 118.3 (CH_2), 72.4 (CH_2), 67.1 (CH_2), 51.8 (OMe).

Methyl 2-methoxyacetate 394



394

To a solution of methoxyacetic acid (5.40 g, 60.0 mmol) in dry methanol (24 mL) and acetone dimethylacetal (96 mL) was added chlorotrimethylsilane (0.77 mL, 6.00 mmol) dropwise over 10 min. The reaction mixture was stirred for 16 h and concentrated *in vacuo* to afford the title compound as a colourless oil (3.72 g, 59%); ν_{max} ($CHCl_3$)/cm^{-1} 1754 (C=O); δ_H (500 MHz; $CDCl_3$) 4.05 (2 H, s, CH_2), 3.77 (3 H, s, OMe), 3.46 (3 H, s, OMe); δ_C (125 MHz; $CDCl_3$) 170.7 (C), 69.7 (CH_2), 59.3 (OMe), 51.8 (OMe).

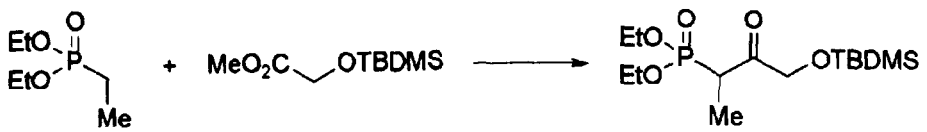
Methyl 2-(4-methoxybenzyloxy)acetate[205] 395

395

To a suspension of sodium hydride (3.12 g, 78.0 mmol) and *para*-methoxybenzyl chloride (12.2 g, 78.0 mmol) in DMF (100 mL) at 0 °C was added methyl glycolate

(7.03 g, 78.0 mmol) dropwise over 30 min. The reaction mixture was allowed to warm to room temperature and stirred for 16 h, then partitioned between water (100 mL) and ether (4 × 100 mL). The combined organics were washed with water (4 × 100 mL) and saturated brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the title compound as a colourless oil (7.81 g, 48%); ν_{max} ($CHCl_3$)/cm^{-1} 1752 (C=O), 1613 (C=C), 1587 (C=C), 1514 (C=C); δ_H (500 MHz; $CDCl_3$) 7.29 (2 H, d, J = 8.5 Hz, ArH), 6.89 (2 H, d, J = 8.5 Hz, ArH), 4.57 (2 H, s, CH_2), 4.08 (2 H, s, CH_2), 3.81 (3 H, s, OMe), 3.77 (3 H, s, OMe); δ_C (125 MHz; $CDCl_3$) 170.9 (C), 159.6 (C), 129.8 (CH), 129.1 (C), 113.9 (CH), 73.0 (CH_2), 66.8 (CH_2), 55.3 (OMe), 51.9 (OMe);

Diethyl 4-(tert-butyldimethylsilyloxy)-3-oxobutan-2-ylphosphonate 396

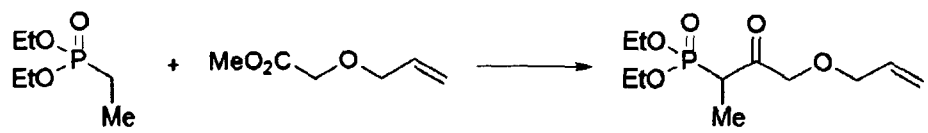


391 **392** **396**

Following general procedure 13, the title compound was obtained from diethyl ethyl phosphonate **391** (0.233 g, 1.40 mmol) and methyl 2-(*tert*-butyldimethylsilyloxy)acetate **392** (0.315 g, 1.54 mmol) as a colourless oil (0.295 g, 62%); (Found: MH^+, 339.1732. $C_{14}H_{32}O_5PSi$ + H requires $C_{14}H_{32}O_5PSi$); ν_{max} ($CHCl_3$)/cm^{-1} 1735 (C=O), 1253 (P=O), 1026 (P-O); δ_H (400 MHz; $CDCl_3$) 4.49 (1 H, d, J = 17.9 Hz, C$\underline{H_2}$), 4.31 (1 H, d, J = 17.9 Hz, C$\underline{H_2}$), 4.19-4.09 (4 H, m, 2 × $POCH_2$), 3.51 (1 H, dq, J = 24.6 Hz and 7.1 Hz, PCH), 1.32-1.29 (6 H, m, 2 × $POCH_2\underline{Me}$), 0.90 (9 H, s, CMe_3), 0.08 (6 H, s, $SiMe_2$); δ_C (100 MHz; $CDCl_3$) 205.1 (d, $^2J_{C\text{-}P}$ = 4.4 Hz, C), 69.5 (CH_2), 62.7 (d, $^2J_{C\text{-}P}$ = 6.7 Hz, $POCH_2$), 62.5 (d, $^2J_{C\text{-}P}$ = 6.7 Hz, $POCH_2$), 41.3

(d, $^{1}J_{C\text{-}P}$ = 128.7 Hz, PCH), 25.8 (C<u>Me</u>$_3$), 18.4 (<u>C</u>Me$_3$), 16.4 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, POCH$_2$<u>Me</u>), 16.3 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, POCH$_2$<u>Me</u>), -5.5 (SiMe$_2$); *m/z* (ESI) 361 (MNa^+, 100%), 339 (MH^+, 89).

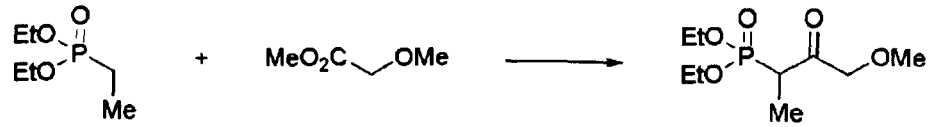
Diethyl 4-(allyloxy)-3-oxobutan-2-ylphosphonate 397



391 **393** **397**

Following general procedure 13, the title compound was obtained from diethyl ethylphosphonate **391** (2.99 g, 18.0 mmol) and methyl 2-(allyloxy)acetate **393** (2.58 g, 19.8 mmol) as a colourless oil (2.94 g, 62%). Found: MH^+, 265.1190. $C_{11}H_{21}O_5P$ + H requires 265.1199); ν_{max} ($CHCl_3$)/cm^{-1} 1721 (C=O), 1241 (P=O), 1026 (P-O); δ_H (400 MHz; $CDCl_3$) 5.96-5.86 (1 H, m, C<u>H</u>=CH$_2$), 5.30 (1 H, ddt, *J* = 17.2, 1.6 and 1.5, CH=C<u>H</u>$_2$), 5.23 (1 H, ddt, *J* = 10.4, 1.6 and 1.5, CH=C<u>H</u>$_2$), 4.36 (1 H, d, *J* = 17.2 Hz, C<u>H</u>$_2$), 4.19 (1 H, d, *J* = 17.2 Hz, C<u>H</u>$_2$), 4.15-4.10 (4 H, m, 2 × CH$_2$), 4.08-4.06 (2 H, m, CHC<u>H</u>$_2$), 3.43 (1 H, dq, *J* = 25.2 and 6.8 Hz, PCH), 1.39-1.29 (9 H, m, 3 × Me); δ_C (100 MHz; $CDCl_3$) 203.6 (d, $^{2}J_{C\text{-}P}$ = 4.4 Hz, C), 133.8 (CH), 118.4 (CH$_2$), 74.9 (CH$_2$), 72.3 (CH$_2$), 63.3 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz, CH$_2$), 63.0 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz, CH$_2$), 42.8 (d, $^{1}J_{C\text{-}P}$ = 127.0 Hz, PCH), 16.7 (d, $^{3}J_{C\text{-}P}$ = 5.9 Hz, 2 × Me), 10.9 (d, $^{2}J_{C\text{-}P}$ = 6.6 Hz, Me); *m/z* (ESI) 287 (MNa^+, 100%), 265 (MH^+, 23).

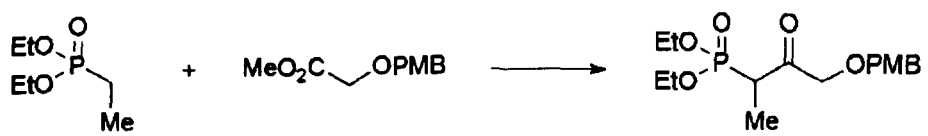
Diethyl 4-methoxy-3-oxobutan-2-ylphosphonate 398



391 **394** **398**

Following general procedure 13, the title compound was obtained from diethyl ethylphosphonate **391** (9.97 g, 60.0 mmol) and methyl 2-methoxyacetate **394** (6.87 g, 66.0 mmol) as a colourless oil (12.1 g, 85%); ν_{max} ($CHCl_3$)/cm^{-1} 1731 (C=O), 1241 (P=O); δ_H (400 MHz; $CDCl_3$) 4.34 (1 H, d, J = 17.2 Hz, C$\underline{H}_2$), 4.18-4.10 (5 H, m, 2 × CH_2 + C$\underline{H}_2$), 3.43 (3 H, s, OMe), 3.41 (1 H, dq, J = 25.2 and 7.2 Hz, PCH), 1.36-1.32 (9 H, m, 3 × Me); δ_C (100 MHz; $CDCl_3$) 203.5 (d, $^2J_{C\text{-}P}$ = 4.2 Hz, C), 77.4 (CH_2), 62.9 (d, $^2J_{C\text{-}P}$ = 6.6 Hz, CH_2), 62.8 (d, $^2J_{C\text{-}P}$ = 6.6 Hz, CH_2), 59.2 (OMe), 42.5 (d, $^1J_{C\text{-}P}$ = 127.0 Hz, CH), 16.8 (d, $^3J_{C\text{-}P}$ = 5.8 Hz, 2 × Me), 10.9 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, Me).

Diethyl 4-(4-methoxybenzyloxy)-3-oxobutan-2-ylphosphonate 399

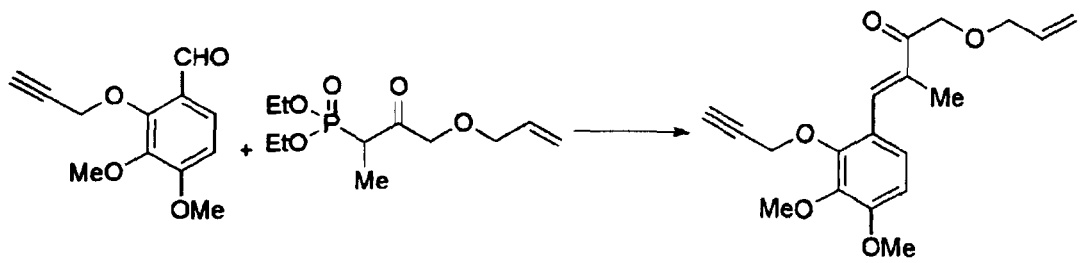


391 **395** **399**

Following general procedure 13, the title compound was obtained from diethyl ethylphosphonate **391** (4.98 g, 30.0 mmol) and methyl 2-(4-methoxybenzyloxy)acetate **395** (6.94 g, 33.0 mmol) as a colourless oil (7.98 g, 77%); (Found: MH^+, 345.1451. $C_{16}H_{25}O_6P$ + H requires 345.1462); ν_{max} ($CHCl_3$)/cm^{-1} 1730 (C=O), 1612 (C=C), 1586 (C=C), 1514 (C=C), 1240 (P=O), 1024 (P-O); δ_H (400 MHz; $CDCl_3$) 7.30 (2 H, d, J = 8.7 Hz, ArH), 6.88 (2 H, d, J = 8.7 Hz, ArH), 4.54 (2 H, s, CH_2), 4.37 (1 H, d, J = 17.2 Hz, C$\underline{H}_2$), 4.20 (1 H, d, J = 17.2 Hz, C$\underline{H}_2$), 4.16-4.06 (4 H, m, 2 × $POCH_2$), 3.81 (3 H, s, OMe), 3.44 (1 H, dq, J = 25.1 and 7.1 Hz, CH), 1.37-1.24 (11 H, m, 3 × Me); δ_C

(100 MHz; $CDCl_3$) 203.7 (d, $^2J_{C\text{-}P}$ = 4.4 Hz, C), 159.5 (C), 129.7 (CH), 129.3 (C), 113.9 (CH), 74.7 (CH_2), 73.1 (CH_2), 62.7 (d, $^2J_{C\text{-}P}$ = 6.8 Hz, $POCH_2$), 62.6 (d, $^2J_{C\text{-}P}$ = 6.8 Hz, $POCH_2$), 55.3 (OMe), 42.5 (d, $^1J_{C\text{-}P}$ = 127.7 Hz, PCH), 16.4 (2 × Me), 10.5 (d, $^2J_{C\text{-}P}$ = 6.6 Hz, Me); *m/z* (ESI) 367 (MNa^+, 100%), 345 (MH^+, 1).

(*E*)-1-(Allyloxy)-4-(3,4-dimethoxy-2-(prop-2-ynyloxy)phenyl)-3-methylbut-3-en-2-one 401

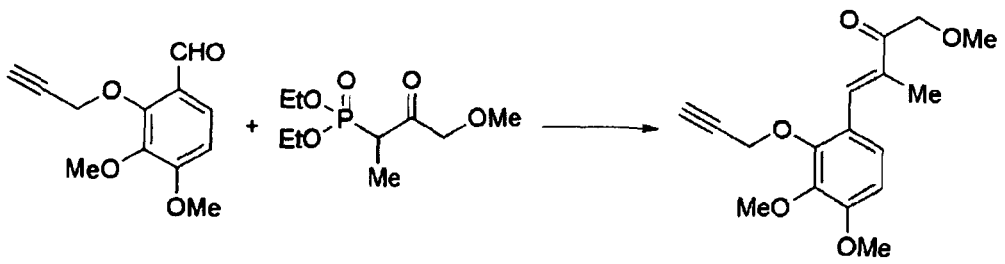


318 **397** **401**

Following general procedure 7, the *title compound* was obtained from 3,4-dimethoxy-2-(prop-2-ynyloxy)benzaldehyde **318** (1.46 g, 6.63 mmol), potassium *tert*-butoxide (1.12 g, 9.95 mmol) and diethyl 4-(allyloxy)-3-oxobutan-2-ylphosphonate **397** (2.63 g, 9.95 mmol) as a colourless oil (0.840 g, 38%); (Found: MH^+, 331.1522. $C_{19}H_{22}O_5$ + H requires 331.1540); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C-H), 2126 (C≡C), 1719 (C=O), 1623 (C=C), 1596 (C=C), 1497 (C=C), 1097 (C-O); δ_H (400 MHz; $CDCl_3$) 7.73 (1 H, s, C=CH), 7.17 (1 H, d, *J* = 8.8 Hz, ArH), 6.76 (1 H, d, *J* = 8.8 Hz, ArH), 6.02-5.93 (1 H, m, C<u>H</u>=CH_2), 5.34 (1 H, ddt, *J* = 17.2, 1.6 and 1.5 Hz, CH=C<u>H</u>$_2$), 5.24 (1 H, ddt, *J* = 10.4, 1.6 and 1.2 Hz, CH=C<u>H</u>$_2$), 4.77 (2 H, d, *J* = 2.4 Hz, CH_2), 4.66 (2 H, s, CH_2), 4.15-4.13 (2 H, m, CHC<u>H</u>$_2$), 3.89 (3 H, s, OMe), 3.87 (3 H, s, OMe), 2.48 (1 H, t, *J* = 2.4 Hz, C≡CH), 2.04 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 197.9 (C), 154.4 (C), 150.4 (C), 142.2 (C), 134.6 (CH), 134.5 (C), 134.3 (CH), 125.1 (CH), 123.1 (C), 117.9

(CH_2), 107.7 (CH), 79.1 (C≡C), 75.6 (C≡C), 72.4 (CH_2), 71.9 (CH_2), 61.0 (CH_2), 60.9 (OMe), 56.1 (OMe), 13.0 (Me); *m/z* (ESI) 353 (MNa^+, 100%), 331 (MH^+, 8).

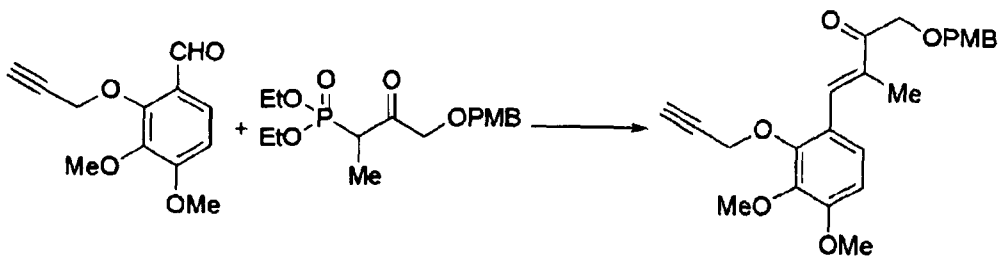
(*E*)-4-(3,4-Dimethoxy-2-(prop-2-ynyloxy)phenyl)-1-methoxy-3-methylbut-3-en-2-one 402



318 **398** **402**

Following general procedure 7, the *title compound* was obtained from 3,4-dimethoxy-2-(prop-2-ynyloxy)benzaldehyde **318** (1.10 g, 5.00 mmol), potassium *tert*-butoxide (0.842 g, 7.50 mmol) and diethyl 4-methoxy-3-oxobutan-2-ylphosphonate **398** (1.79 g, 7.50 mmol) as a colourless oil (0.970 g, 64%); (Found: MH^+, 305.1379. $C_{17}H_{20}O_5$ + H requires 305.1384); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C-H), 1678 (C=O), 1623 (C=C), 1596 (C=C), 1496 (C=C), 1455 (C=C), 1098 (C-O); δ_H (500 MHz; $CDCl_3$) 7.72 (1 H, s, C=CH), 7.17 (1 H, d, J = 8.7 Hz, ArH), 6.75 (1 H, d, J = 8.7 Hz, ArH), 4.78 (2 H, d, J = 2.4 Hz, CH_2), 4.62 (2 H, s, CH_2), 3.90 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.49 (3 H, s, OMe), 2.49 (1 H, t, J = 2.4 Hz, C≡CH), 2.04 (3 H, s, Me); δ_C (125 MHz; $CDCl_3$) 197.8 (C), 154.5 (C), 150.5 (C), 142.2 (C), 134.6 (CH), 134.5 (C), 125.1 (CH), 123.1 (C), 107.8 (C), 107.7 (CH), 79.1 (C≡CH), 75.7 (CH_2), 74.6 (C≡CH), 61.1 (CH_2), 61.0 (OMe), 59.4 (OMe), 56.1 (OMe), 13.0 (Me); *m/z* (ESI) 327 (MNa^+, 100%), 305 (MH^+, 7%).

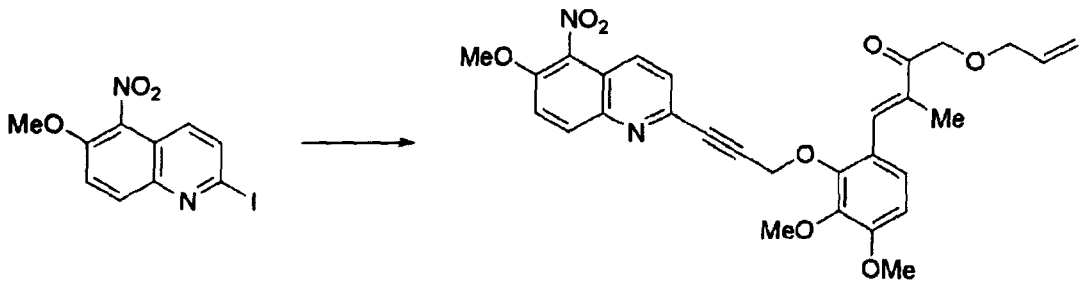
(*E*)-1-(4-Methoxybenzyloxy)-4-(3,4-dimethoxy-2-(prop-2-ynyloxy)phenyl)-3-methylbut-3-en-2-one 403



318 **399** **403**

Following general procedure 7, the *title compound* was obtained from 3,4-dimethoxy-2-(prop-2-ynyloxy)benzaldehyde **318** (2.98 g, 13.6 mmol), potassium *tert*-butoxide (2.29 g, 20.4 mmol) and diethyl 4-(4-methoxybenzyloxy)-3-oxobutan-2-ylphosphonate **399** (7.02 g, 20.4 mmol) as a colourless oil (4.19 g, 75%); (Found: MH^+, 411.1788. $C_{24}H_{26}O_4$ + H requires 411.1802); ν_{max} ($CHCl_3$)/cm^{-1} 3307 (alkyne C-H), 1678 (C=O), 1612 (C=C), 1596 (C=C), 1514 (C=C), 1497 (C=C), 1098 (C-O); δ_H (400 MHz; $CDCl_3$) 7.70 (1 H, s, C=CH), 7.34 (2 H, d, J = 8.8 Hz, ArH), 7.15 (1 H, d, J = 8.8 Hz, ArH), 6.89 (2 H, d, J = 8.8 Hz, ArH), 6.75 (1 H, d, J = 8.8 Hz, ArH), 4.73 (2 H, d, J = 2.4 Hz, CH_2), 4.64 (2 H, s, CH_2), 4.61 (2 H, s, CH_2), 3.89 (3 H, s, OMe), 3.87 (3 H, s, OMe), 3.78 (3 H, s, OMe), 2.36 (1 H, t, J = 2.4 Hz, C≡CH), 2.03 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 198.0 (C), 159.4 (C), 154.4 (C), 150.5 (C), 142.2 (C), 134.7 (CH), 134.5 (C), 129.7 (CH), 125.1 (CH), 123.1 (C), 113.9 (CH), 107.7 (CH), 79.1 (C≡CH), 75.7 (C≡CH), 72.9 (CH_2), 71.6 (CH_2), 61.1 (CH_2), 61.0 (OMe), 56.1 (OMe), 55.3 (OMe), 13.0 (Me); *m/z* (ESI) *m/z* (ESI) 433 (MNa^+, 100%), 411 (MH^+, 2).

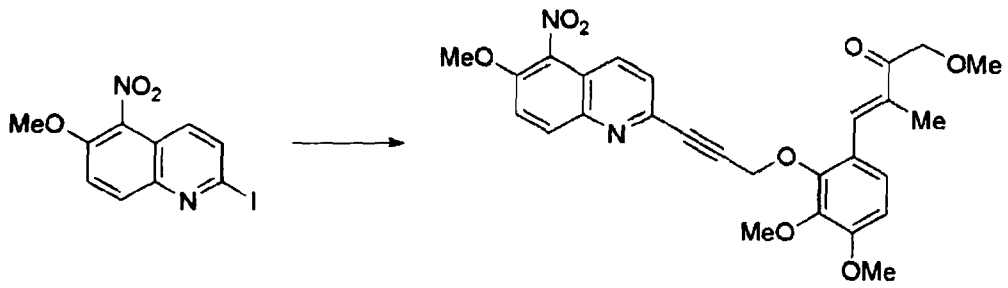
(*E*)-1-(Allyloxy)-4-(3,4-dimethoxy-2-(3-(6-methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)phenyl)-3-methylbut-3-en-2-one 405



317 **405**

Following general procedure 8, the *title compound* was obtained from 2-iodo-6-methoxy-5-nitroquinoline **317** (0.505 g, 1.53 mmol) and alkyne **401** (0.758 g, 2.30 mmol) as a colourless solid (0.668 g, 82%), mp 133-135 °C (from dichloromethane-hexane); (Found: MH^+, 533.1921. $C_{29}H_{28}N_2O_8$ + H requires 533.1918); ν_{max} ($CHCl_3$)/cm^{-1} 1678 (C=O), 1628 (C=C), 1595 (C=C), 1532 (C=C), 1496 (C=C), 1356, (NO_2), 1097 (C-O); δ_H (400 MHz; $CDCl_3$) 8.25 (1 H, d, J = 9.4 Hz, ArH), 8.03 (1 H, d, J = 8.8 Hz, ArH), 7.85 (1 H, s, C=CH), 7.61 (1 H, d, J = 9.4 Hz, ArH), 7.49 (1 H, d, J = 8.8 Hz, ArH), 7.21 (1 H, d, J = 8.8 Hz, ArH), 6.80 (1 H, d, J = 8.8 Hz, ArH), 5.93-5.84 (1 H, m, C=CH), 5.24 (1 H, ddt, J = 17.2, 1.6, and 1.5 Hz, C=C$\underline{H_2}$), 5.14 (1 H, ddt, J = 10.4, 1.6 and 1.2 Hz, C=C$\underline{H_2}$), 5.10 (2 H, s, CH_2), 4.74 (2 H, s, CH_2), 4.10 (3 H, s, OMe), 4.06-4.04 (2 H, m, CH_2), 3.95 (3 H, s, OMe), 3.94 (3 H, s, OMe), 1.59 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 198.0 (C), 154.5 (C), 150.5 (C), 149.9 (C), 142.3 (C), 142.2 (C), 141.7 (C), 134.6 (C), 134.4 (CH), 134.2 (CH), 134.1 (CH), 129.6 (CH), 126.4 (CH), 125.2 (CH), 123.3 (C), 120.4 (C), 117.7 (CH_2), 117.0 (CH), 107.9 (CH), 99.3 (C), 86.5 (C≡C), 86.1 (C≡C), 72.3 (CH_2), 72.1 (CH_2), 61.6 (CH_2), 61.1 (OMe), 57.2 (OMe), 56.1 (OMe), 13.1 (Me); *m/z* (ESI) 555 (MNa^+, 100%), 533 (MH^+, 36).

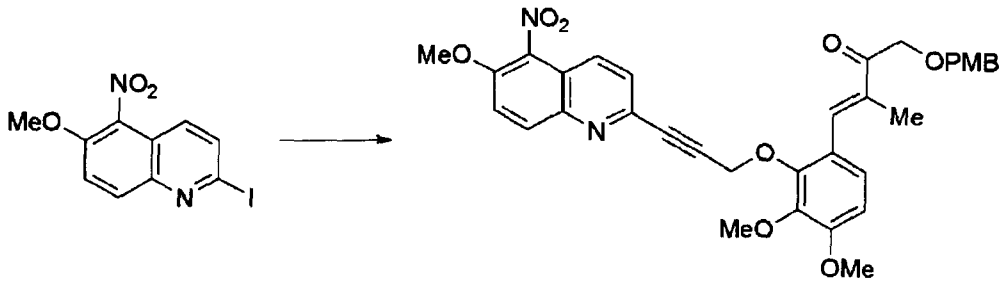
(*E*)-4-(3,4-Dimethoxy-2-(3-(6-methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)phenyl)-1-methoxy-3-methylbut-3-en-2-one 406



317 **406**

Following general procedure 8, the *title compound* was obtained from 2-iodo-6-methoxy-5-nitroquinoline **317** (0.660 g, 2.00 mmol) and alkyne **402** (0.913 g, 3.00 mmol) as a colourless solid (0.754 g, 74%), mp 148-150 °C (from dichloromethane-hexane); (Found: C, 63.93; H, 5.17; N, 5.43. $C_{27}H_{26}N_2O_8$ requires C, 64.02; H, 5.17; N, 5.53%); (Found: MH^+, 507.1764. $C_{27}H_{26}N_2O_8$ + H requires 507.1762); ν_{max} ($CHCl_3$)/cm^{-1} 1677 (C=O), 1628 (C=C), 1595 (C=C), 1532 (C=C), 1495 (C=C), 1461 (C=C), 1356 (NO_2), 1096 (C-O); δ_H (400 MHz; $CDCl_3$) 8.23 (1 H, d, J = 9.6 Hz, ArH), 8.01 (1 H, d, J = 8.8 Hz, ArH), 7.84 (1 H, s, C=CH), 7.60 (1 H, d, J = 9.6 Hz, ArH), 7.48 (1 H, d, J = 8.8 Hz, ArH), 7.20 (1 H, d, J = 8.8 Hz, ArH), 6.79 (1 H, d, J = 8.8 Hz, ArH), 5.09 (2 H, s, CH_2), 4.69 (2 H, s, CH_2), 4.09 (3 H, s, OMe), 3.94 (3 H, s, OMe), 3.93 (3 H, s, OMe), 3.37 (3 H, s, OMe), 2.02 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 197.8 (C), 154.5 (C), 150.5 (C), 149.9 (C), 142.2 (C), 141.7 (C), 134.5 (C), 134.4 (CH), 134.1 (CH), 129.6 (CH), 126.3 (CH), 125.2 (CH), 123.3 (C), 120.4 (C), 117.0 (CH), 108.0 (CH), 86.5 (C≡C), 86.1 (C≡C), 74.7 (CH_2), 61.6 (CH_2), 61.1 (OMe), 59.3 (OMe), 57.2 (OMe), 56.1 (OMe), 13.1 (Me); *m/z* (ESI) 529 (MNa^+, 100%), 507 (MH^+, 46).

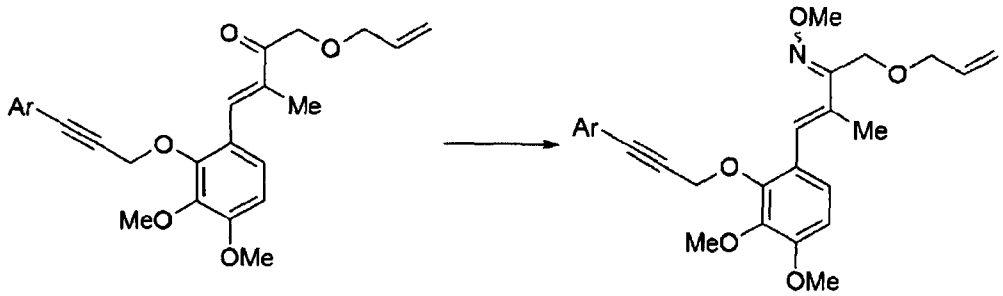
(*E*)-4-(2-(3-(6-Methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)-3,4-dimethoxyphenyl)-1-(4-methoxybenzyloxy)-3-methylbut-3-en-2-one 407



317 **407**

Following general procedure 8, the *title compound* was obtained from 2-iodo-6-methoxy-5-nitroquinoline **317** (1.40 g, 4.24 mmol) and alkyne **403** (2.61 g, 6.36 mmol) as a colourless solid (2.45 g, 94%), mp 125-126 °C (from dichloromethane-hexane); (Found: C, 66.37; H, 5.18; N 4.40. $C_{34}H_{32}N_2O_9$ requires C, 66.66; H, 5.26; N, 4.57%); (Found: MH^+, 613.2165. $C_{34}H_{32}N_2O_9$ + H requires 613.2181); ν_{max} ($CHCl_3$)/cm^{-1} 1677 (C=O), 1628 (C=C), 1613 (C=C), 1595 (C=C), 1531 (C=C), 1514 (C=C), 1496 (C=C), 1096 (C-O); δ_H (400 MHz; $CDCl_3$) 8.18 (1 H, d, J = 9.6 Hz, ArH), 7.98 (1 H, d, J = 8.8 Hz, ArH), 7.84 (1 H, s, C=CH), 7.52 (1 H, d, J = 9.6 Hz, ArH), 7.44 (1 H, d, J = 8.8 Hz, ArH), 7.22 (2 H, d, J = 8.4 Hz, ArH), 7.18 (1 H, d, J = 8.8 Hz, ArH), 6.81 (2 H, d, J = 8.4 Hz, ArH), 6.78 (1 H, d, J = 8.8 Hz, ArH), 5.06 (2 H, s, CH_2), 4.73 (2 H, s, CH_2), 4.48 (2 H, s, CH_2), 4.06 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.77 (3 H, s, OMe), 2.01 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 198.2 (C), 159.3 (C), 154.5 (C), 150.5 (C), 149.9 (C), 142.2 (C), 141.7 (C), 134.7 (C), 57.2 (OMe), 134.5 (CH), 134.2 (CH), 129.7 (C), 129.6 (CH), 126.3 (CH), 125.2 (CH), 123.3 (C), 120.3 (C), 117.1 (CH), 116.9 (CH), 113.7 (CH), 107.9 (CH), 72.9 (CH_2), 72.0 (CH_2), 61.6 (CH_2), 61.1 (OMe), 56.1 (OMe), 55.2 (OMe), 13.1 (Me); *m/z* (ESI) 635 (MNa^+, 100%), 613 (MH^+, 36).

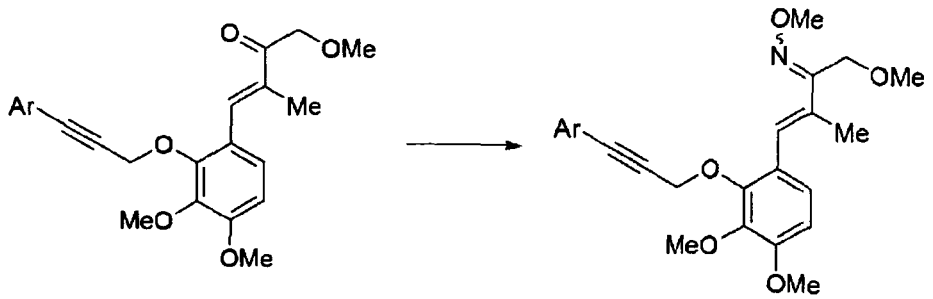
(*E*)-1-(Allyloxy)-4-(3,4-dimethoxy-2-(3-(6-methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)phenyl)-3-methylbut-3-en-2-one *O*-methyl oxime 409



405 Ar = 6-methoxy-5-nitroquinolin-2-yl **409**

Following general procedure 9, the *title compound* was prepared from ketone **405** (0.400 g, 0.751 mmol), methoxylamine hydrochloride (0.078 g, 0.939 mmol) and sodium acetate trihydrate (0.107 g, 0.789 mmol) as an orange solid (0.422 g, 100%), mp 78-80 °C (from dichloromethane-hexane); (Found: MH^+, 562.2171. $C_{30}H_{31}N_3O_8$ + H requires 562.2184); ν_{max} ($CHCl_3$)/cm^{-1} 1628 (C=C), 1597 (C=C), 1531 (C=C), 1495 (C=C), 1462 (C=C), 1357 (N=O), 1097 (C-O); δ_H (400 MHz; $CDCl_3$) 8.18 (1 H, d, J = 9.5 Hz, ArH), 7.97 (1 H, d, J = 8.8 Hz, ArH), 7.56 (1 H, d, J = 9.5 Hz, ArH), 7.51 (1 H, d, J = 8.8 Hz, ArH), 7.23 (1 H, s, C=CH), 7.03 (1 H, d, J = 8.7 Hz, ArH), 6.72 (1 H, d, J = 8.7 Hz, ArH), 5.95-5.83 (1 H, m, C<u>H</u>=CH_2), 5.25 (1 H, ddt, J = 17.2, 1.6 and 1.5 Hz, CH=C<u>H</u>$_2$), 5.12 (1 H, ddt, J = 17.2, 1.6 and 1.2 Hz, CH=C<u>H</u>$_2$), 5.00 (2 H, s, CH_2), 4.51 (2 H, s, CH_2), 4.05 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.88 (3 H, s, OMe), 2.00 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 157.1 (C), 153.0 (C), 149.9 (C), 149.7 (C), 142.3 (C), 142.1 (C), 142.0 (C), 134.6 (CH), 134.0 (CH), 132.3 (C), 129.4 (C), 129.3 (CH), 127.2 (CH), 126.7 (CH), 126.6 (C), 125.1 (CH), 120.3 (C), 117.4 (CH_2), 116.8 (CH), 107.6 (CH), 86.9 (C≡C), 85.9 (C≡C), 71.9 (CH_2), 62.1 (OMe), 61.2 (OMe), 61.1 (CH_2), 60.0 (CH_2), 57.2 (OMe), 56.0 (OMe), 14.6 (Me); *m/z* (ESI) 584 (MNa^+, 96%), 562 (MH^+, 100).

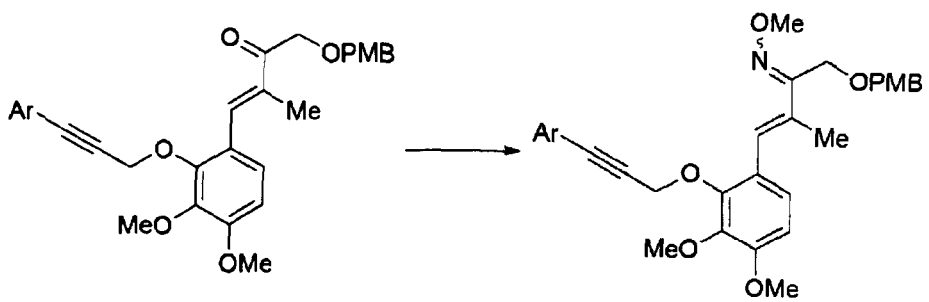
(*E*)-4-(3,4-Dimethoxy-2-(3-(6-methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)phenyl)-1-methoxy-3-methylbut-3-en-2-one *O*-methyl oxime 410



406 Ar = 6-methoxy-5-nitroquinolin-2-yl **410**

Following general procedure 9, the *title compound* was obtained from ketone **406** (0.600 g, 1.18 mmol), methoxylamine hydrochloride (0.123 g, 1.48 mmol) and sodium acetate trihydrate (0.169 g, 1.24 mmol) as a colourless solid (0.376 g, 59%), mp 73-75 °C (from dichloromethane-hexane); (Found: MH^+, 536.2019. $C_{28}H_{30}N_3O_8$ + H requires 536.2027); ν_{max} ($CHCl_3$)/cm^{-1} 2253 (C≡C), 1628 (C=C), 1596 (C=C), 1531 (C=C), 1495 (C=C), 1463 (C=C), 1357 (N=O), 1097 (C-O); δ_H (500 MHz; $CDCl_3$) 8.18 (1 H, d, *J* = 9.5 Hz, ArH), 7.98 (1 H, d, *J* = 8.8 Hz, ArH), 7.56 (1 H, d, *J* = 9.5 Hz, ArH), 7.51 (1 H, d, *J* = 8.8 Hz, ArH), 7.21 (1 H, s, C=CH), 7.05 (1 H, d, *J* = 8.7 Hz, ArH), 6.72 (1 H, d, J = 8.7 Hz, ArH), 5.00 (2 H, s, CH_2), 4.46 (2 H, s, CH_2), 4.07 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.34 (3 H, s, OMe), 2.01 (3 H, s, Me); δ_C (125 MHz; $CDCl_3$) 157.0 (C), 153.1 (C), 150.0 (C), 149.8 (C), 142.4 (C), 142.2 (C), 134.0 (CH), 132.3 (C), 129.4 (CH), 127.1 (CH), 126.7 (CH), 125.1 (CH), 124.8 (C), 120.3 (C), 116.8 (CH), 107.7 (CH), 86.9 (C≡CH), 86.0 (C≡CH), 62.5 (CH_2), 62.2 (OMe), 61.2 (OMe), 61.1 (CH_2), 58.7 (OMe), 57.3 (OMe), 56.1 (OMe), 14.6 (Me); *m/z* (ESI) 558 (MNa^+, 100%), 536 (MH^+, 94).

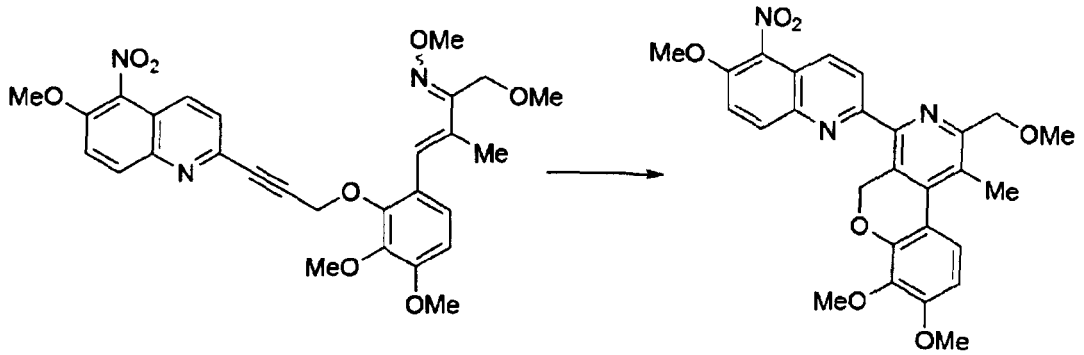
(*E*)-4-(2-(3-(6-Methoxy-5-nitroquinolin-2-yl)prop-2-ynyloxy)-3,4-dimethoxyphenyl)-1-(4-methoxybenzyloxy)-3-methylbut-3-en-2-one *O*-methyl oxime 411



407 Ar = 6-methoxy-5-nitroquinolin-2-yl **411**

Following general procedure 9, the *title compound* was obtained from ketone **407** (2.30 g, 3.75 mmol), methoxylamine hydrochloride (0.392 g, 4.69 mmol) and sodium acetate trihydrate (0.536 g, 3.94 mmol) as a colourless solid (2.30 g, 84%), mp 76-78 °C (from dichloromethane-hexane); (Found: MH^+, 642.2447. $C_{35}H_{35}N_3O_9$ + H requires 642.2446); ν_{max} ($CHCl_3$)/cm^{-1} 1677 (C=O), 1628 (C=C), 1613 (C=C), 1595 (C=C), 1531 (C=C), 1514 (C=C), 1496 (C=C), 1096 (C-O); δ_H (400 MHz; $CDCl_3$) 8.16 (1 H, d, *J* = 9.6 Hz, ArH), 7.91 (1 H, d, *J* = 8.8 Hz, ArH), 7.55 (1 H, d, *J* = 9.6 Hz, ArH), 7.45 (1 H, d, *J* = 8.8 Hz, ArH), 7.25 (1 H, s, C=CH), 7.24 (2 H, d, *J* = 8.4 Hz, ArH), 7.05 (1 H, d, *J* = 8.8 Hz, ArH), 6.81 (2 H, d, *J* = 8.4 Hz, ArH), 6.74 (1 H, d, *J* = 8.8 Hz, ArH), 4.98 (2 H, s, CH_2), 4.54 (2 H, s, CH_2), 4.47 (2 H, s, CH_2), 4.07 (3 H, s, OMe), 3.95 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.89 (3 H, s, OMe), 3.75 (3 H, s, OMe), 2.02 (3 H, s, Me); δ_C (100 MHz;$CDCl_3$) 159.1 (C), 157.3 (C), 153.0 (C), 150.0 (C), 149.7 (C), 142.4 (C), 142.1 (C), 142.0 (C), 134.0 (CH), 130.2 (C), 129.5 (CH), 129.3 (CH), 127.3 (CH), 126.7 (CH), 125.1 (CH), 124.9 (C), 120.3 (C), 116.7 (CH), 113.6 (CH), 107.7 (CH), 86.9 (C≡C), 86.0 (C≡C), 72.5 (CH_2), 62.1 (OMe), 61.2 (OMe), 61.1 (CH_2), 60.0 (CH_2), 57.2 (OMe), 56.1 (OMe), 55.2 (OMe), 53.4 (OMe), 14.7 (Me); *m/z* (ESI) 664 (MNa^+, 99%), 642 (MH^+, 100).

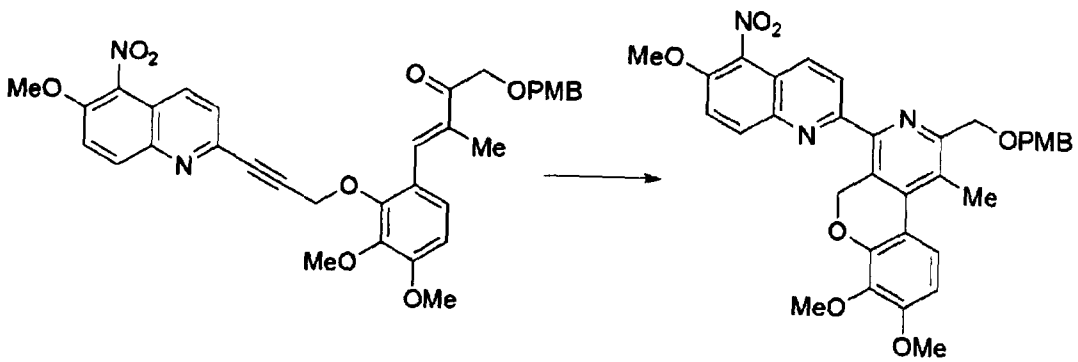
7,8-Dimethoxy-4-(6-methoxy-5-nitroquinolin-2-yl)-2-(methoxymethyl)-1-methyl-5*H*-chromeno[3,4-c]pyridine 414



410 **414**

Following general procedure 11, the *title compound* was obtained from oxime **410** (0.300 g, 0.560 mmol) after 16 h at reflux in xylene as a colourless solid (0.115 g, 41%), mp 205-207 °C (from dichloromethane-hexane); (Found: MH^+, 504.1759. $C_{27}H_{25}N_3O_7$ + H requires 504.1765); ν_{max} ($CHCl_3$)/cm^{-1} 1629 (C=C), 1600 (C=C), 1551 (C=C), 1531 (C=C), 1499 (C=C), 1463 (C=C), 1355 (N=O), 1105 (C-O); δ_H (400 MHz; $CDCl_3$) 8.57 (1 H, d, *J* = 9.2 Hz, ArH), 8.24 (1 H, d, *J* = 9.6 Hz, ArH), 8.19 (1 H, d, *J* = 8.8 Hz, ArH), 7.59 (1 H, d, *J* = 9.6 Hz, ArH), 7.49 (1 H, d, J = 8.8 Hz, ArH), 6.75 (1 H, d, *J* = 8.8 Hz, ArH), 5.65 (2 H, s, CH_2), 4.80 (2 H, s, CH_2), 4.09 (3 H, s, OMe), 3.97 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.51 (3 H, s, OMe), 2.70 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.8 (C), 155.7 (C), 154.1 (C), 149.5 (C), 141.2 (C), 138.1 (C), 134.1 (CH), 129.6 (CH), 129.3 (C), 128.5 (C), 124.3 (CH), 124.1 (CH), 120.5 (C), 117.1 (C), 116.2 (CH), 105.5 (CH), 76.0 (CH_2), 67.5 (CH_2), 61.4 (OMe), 58.5 (OMe), 57.2 (OMe), 56.1 (OMe), 17.3 (Me); *m/z* (ESI) 526 (MNa^+, 19%), 504 (MH^+, 100).

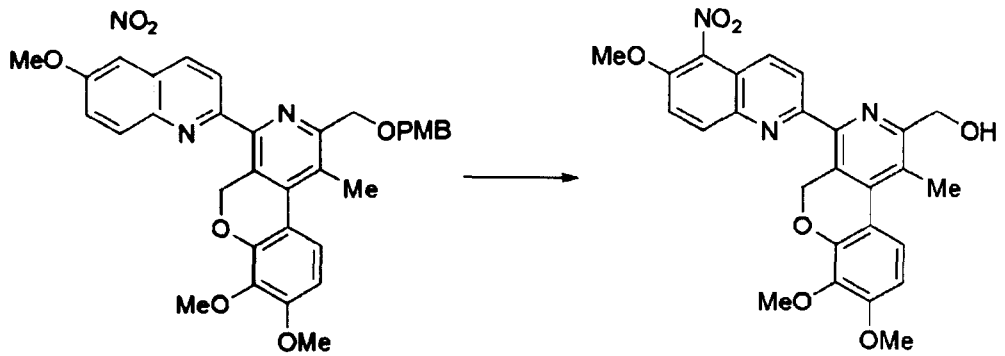
7,8-Dimethoxy-4-(6-methoxy-5-nitroquinolin-2-yl)-2-((4-methoxybenzyloxy)methyl)-1-methyl-5H-chromeno[3,4-c]pyridine 415



411 **415**

Following general procedure 11, the *title compound* was obtained from ketone **411** (0.250 g, 0.408 mmol), methoxylamine hydrochloride (0.068 g, 0.816 mmol) and triethylamine (0.113 mL, 0.816 mmol) after 16 h at reflux in xylene as a colourless solid (0.094 g, 38%), mp 199-201 °C (from dichloromethane-hexane); (Found: MH^+, 610.2168. $C_{34}H_{31}N_3O_8$ + H requires 610.2184); ν_{max} ($CHCl_3$)/cm^{-1} 1629 (C=C), 1601 (C=C), 1571 (C=C), 1550 (C=C), 1531 (C=C), 1513 (C=C), 1499 (C=C), 1464 (C=C), 1355 (N=O), 1105 (C-O); δ_H (400 MHz; $CDCl_3$) 8.58 (1 H, d, J = 9.2 Hz, ArH), 8.25 (1 H, d, J = 9.6 Hz, ArH), 8.21 (1 H, d, J = 9.2 Hz, ArH), 7.60 (1 H, d, J = 9.6 Hz, ArH), 7.49 (1 H, d, J = 8.8 Hz, ArH), 7.33 (2 H, d, J = 8.8 Hz, ArH), 6.90 (2 H, d, J = 8.8 Hz, ArH), 6.75 (1 H, d, J = 8.8 Hz, ArH), 5.66 (2 H, s, CH_2), 4.87 (2 H, s, CH_2), 4.60 (2 H, s, CH_2), 4.11 (3 H, s, OMe), 3.97 (3 H, s, OMe), 3.94 (3 H, s, OMe), 3.82 (3 H, s, OMe), 2.69 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 159.4 (C), 155.0 (C), 154.7 (C), 154.5 (C), 151.5 (C), 149.9 (C), 146.8 (C), 141.3 (C), 134.7 (C), 134.2 (CH), 129.8 (CH), 129.6 (C), 129.3 (C), 124.4 (CH), 124.2 (CH), 120.7 (C), 116.6 (CH), 113.8 (CH), 105.3 (CH), 72.7 (CH_2), 71.9 (CH_2), 67.1 (CH_2), 61.4 (OMe), 57.3 (OMe), 56.1 (OMe), 55.3 (OMe), 17.5 (Me); *m/z* (ESI) 632 (MNa^+, 39%), 610 (MH^+, 90), 362 (13), 288 (16), 242 (100).

(7,8-Dimethoxy-4-(6-methoxy-5-nitroquinolin-2-yl)-1-methyl-5*H*-chromeno[3,4-c]pyridin-2-yl)methanol 416

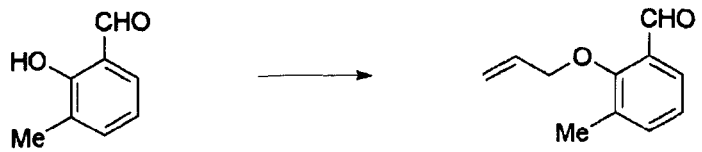


415 **416**

To a solution of *para*-methoxybenzyl protected pyridine **415** (0.240 g, 0.394 mmol) in dichloromethane (2 mL) at 0 °C was added anisole (0.4 mL) and trifluoacetic acid (2 mL). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was removed *in vacuo*, and the residue partitioned between water (20 mL) and dichloromethane (3 × 20 mL). The combined organics were washed with saturated brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (2:3) to afford the *title compound* as a colourless solid (0.168 g, 87%), mp 218-220 °C (from dichloromethane-hexane); (Found: MH^+, 490.1595. $C_{26}H_{23}N_3O_7$ + H requires 490.1609); ν_{max} ($CHCl_3$)/cm^{-1} 3389 (O-H), 1628 (C=C), 1601 (C=C), 1579 (C=C), 1554 (C=C), 1531 (C=C), 1499 (C=C), 1463 (C=C), 1358 (N=O), 1105 (C-O); δ_H (500 MHz; $CDCl_3$) 8.50 (1 H, d, J = 9.5 Hz, ArH), 8.24 (1 H, d, J = 8.5 Hz, ArH), 8.22 (1 H, d, J = 8.5 Hz, ArH), 7.61 (1 H, d, J = 9.5 Hz, ArH), 7.43 (1 H, d, J = 9.0 Hz, ArH), 6.74 (1 H, d, J = 9.0 Hz, ArH), 5.66 (2 H, s, CH_2), 4.86 (2 H, s, CH_2), 4.12 (3 H, s, OMe), 3.97 (3 H, s, OMe), 3.95 (3 H, s, OMe), 2.50 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 156.1 (C), 155.8 (C), 154.3 (C), 151.5 (C), 149.7 (C), 147.0 (C), 141.2 (C), 139.6 (C), 138.1 (C), 134.8 (C), 134.2 (CH), 129.9 (CH), 128.6 (C), 124.8

(C), 124.0 (CH), 123.9 (CH), 120.6 (C), 116.7 (C), 116.4 (CH), 105.2 (CH), 67.5 (CH_2), 62.0 (CH_2), 61.4 (OMe), 57.3 (OMe), 56.1 (OMe), 15.3 (Me); *m/z* (ESI) 512 (MNa^+, 31%), 490 (MH^+, 95), 288 (16), 242 (100).

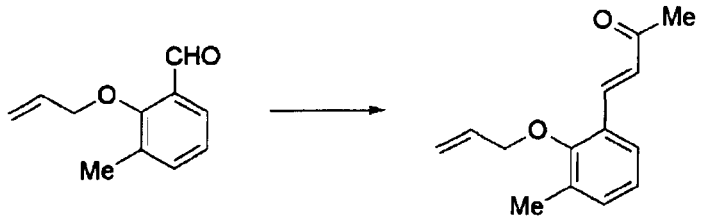
2-(Allyloxy)-3-methylbenzaldehyde[206] 419



312 **419**

Following general procedure 6, the title compound was obtained from 3-methylsalicaldehyde **321** (8.17 g, 60.0 mmol), potassium carbonate (12.4 g, 90.0 mmol) and allyl bromide (26.0 mL, 300 mmol) as a colourless oil (10.6 g, 100%); ν_{max} ($CHCl_3$)/cm^{-1} 1678 (C=O), 1590 (C=C), 1471 (C=C), 1392 (C=C), 1086 (C-O); δ_H (400 MHz; $CDCl_3$) 10.38 (1 H, s, CHO), 7.69 (1 H, d, J = 7.6 Hz, ArH), 7.45 (1 H, d, J = 7.6 Hz, ArH), 7.14 (1 H, t, J = 7.6 Hz, ArH), 6.14 - 6.07 (1 H, m, CH), 5.43 (1 H, dd, J = 17.2 and 1.2 Hz, CH), 5.31 (1 H, dd, J = 10.4 and 1.2 Hz, CH), 4.47 (2 H, dd, J = 5.6 and 1.2 Hz, CH_2), 2.35 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 190.5 (CHO), 160.4 (C), 137.5 (CH), 132.7 (CH), 132.5 (C), 129.5 (C), 126.4 (CH), 124.4 (CH), 118.7 (CH_2), 76.5 (CH_2), 15.9 (Me);

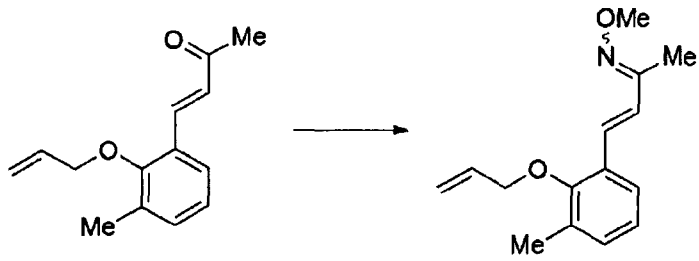
(*E*)-4-(2-(Allyloxy)-3-methylphenyl)but-3-en-2-one



419

Following general procedure 7, the *title compound* was obtained from 2-(allyloxy)-3-methylbenzaldehyde **419** (6.17 g, 35.0 mmol), potassium *tert*-butoxide (5.89 g, 52.5 mmol) and dimethyl 2-oxopropylphosphonate **324** (8.72 g, 52.5 mmol) as a colourless oil (7.05 g, 93%); (Found: MNa^+, 239.1043. $C_{14}H_{16}O_2$ + Na requires 239.1043); ν_{max} ($CHCl_3$)/cm^{-1} 1688 (C=O), 1644 (C=C), 1622 (C=C), 1606 (C=C), 1588 (C=C), 1464 (C=C), 1090 (C-O); δ_H (400 MHz; $CDCl_3$) 7.86 (1 H, d, J = 13.2 Hz, C=CH), 7.44 (1 H, d, J = 6.0 Hz, ArH), 7.25 (1 H, d, J = 6.0 Hz, ArH), 7.07 (1 H, t, J = 6.0 Hz, ArH), 6.71 (1 H, d, J = 13.2 Hz, C=CH), 6.15 - 6.09 (1 H, m, CH), 5.47 (1 H, dd, J = 13.6 and 1.3 Hz, CH=C$\underline{H_2}$), 5.37 (1 H, dd, J = 10.4, and 1.3 Hz, CH=C$\underline{H_2}$), 4.35 (2 H, m, CH_2), 2.39 (3 H, s, Me), 2.33 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 198.9 (C), 156.8 (C), 139.0 (CH), 133.5 (CH), 133.4 (CH), 133.3 (C), 132.1 (C), 128.2 (CH), 128.1 (C), 125.2 (CH), 124.5 (CH), 117.8 (CH_2), 74.9 (CH_2), 27.0 (Me), 16.2 (Me); *m/z* (ESI) 239 (MNa^+, 100%).

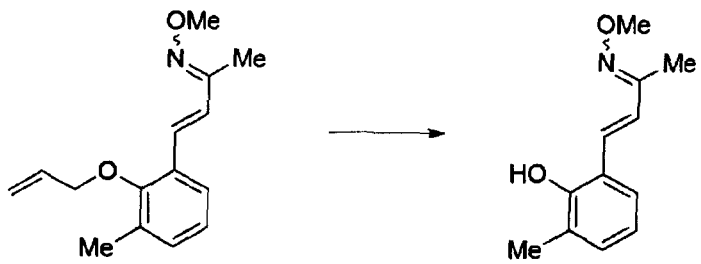
(3*E*)-4-(2-(Allyloxy)-3-methylphenyl)but-3-en-2-one *O*-methyl oxime 420



420

Following general procedure 9, the *title compound* was obtained from the ketone (9.00 g, 41.6 mmol), methoxylamine hydrochloride (4.34 g, 52.0 mmol) and sodium acetate trihydrate (5.94 g, 43.7 mmol) as a colourless oil (9.70 g, 95%); (Found: MH^+, 246.1489. $C_{15}H_{19}NO_2$ + H requires 246.1489); ν_{max} ($CHCl_3$)/cm^{-1} 1647 (C=N), 1620 (C=C), 1587 (C=C), 1463 (C=C), 1089 (C-O); δ_H (400 MHz; $CDCl_3$) 7.44 (1 H, d, J = 7.6 Hz ArH), 7.22 (1 H, d, J = 16.4 Hz, C=CH), 7.13 (1 H, d, J = 7.6 ArH), 7.03 (1 H, t, J = 7.6 Hz, ArH), 6.83 (1 H, d, J = 16.4 Hz, C=CH), 6.15 - 6.08 (1 H, m, C<u>H</u>=CH_2), 5.46 (1 H, dt, J = 16.8 and 1.2 Hz, CH=C<u>H</u>$_2$), 5.30 (1 H, dt, J = 10.4 and 1.2 Hz, C=C<u>H</u>$_2$), 4.33 (2 H, m, CH_2), 3.97 (3 H, s, OMe), 2.31 (3 H, s, Me), 2.08 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.1 (CN), 155.5 (C), 133.7 (CH), 131.7 (C), 131.2 (CH), 130.2 (C), 127.9 (CH), 126.6 (CH), 124.3 (CH), 123.9 (CH), 117.4 (C=<u>C</u>H_2), 74.5 (CH_2), 61.9 (OMe), 16.2 (Me), 10.1 (Me); *m/z* (ESI) 268 (MNa^+, 64%), 246 (MH^+, 100%).

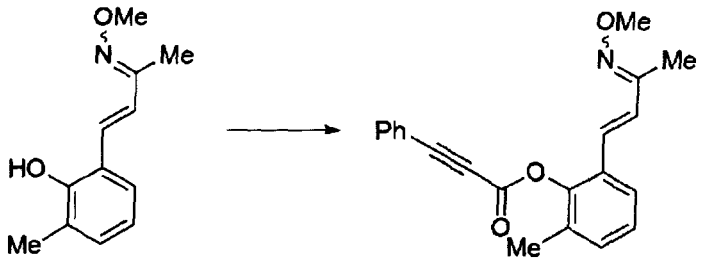
(*E*)-4-(2-hydroxy-3-methylphenyl)but-3-en-2-one *O*-methyl oxime 421



420 **421**

To a solution of oxime **420** (9.00 g, 36.7 mmol), palladium(II) acetate (0.823 g, 3.67 mmol) and triphenylphosphine (14.4 g, 55.1 mmol) in THF (150 mL) was added morpholine (3.86 mL, 44.0 mmol) dropwise over 15 min. The reaction mixture was stirred at room temperature for 14 h. The solvent was removed *in vacuo* and the residue purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9 to 1:4) to afford the *title compound* as a colourless solid (6.18 g, 82%); 138-140 °C (from dichloromethane-hexane); (Found: C, 69.95; H, 7.38; N, 6.78. $C_{12}H_{15}NO_2$ requires C, 70.22; H, 7.37; N, 6.82%); (Found: MH^+, 206.1171. $C_{12}H_{15}NO_2$ + H requires 206.1176); ν_{max} ($CHCl_3$)/cm^{-1} 3606 (O-H), 1591 (C=C), 1465 (C=C), 1436 (C=C), 1057 (C-O); δ_H (400 MHz; $CDCl_3$) 7.34 (1 H, d, J = 7.6 Hz, ArH), 7.20 (1 H, d, J = 16.5 C=CH), 7.07 (1 H, d, J = 7.6 Hz, ArH), 6.85 (1 H, t, J = 7.6 Hz, ArH), 6.83 (1 H, d, J = 16.5 Hz, C=CH), 5.02 (1 H, s, OH), 3.96 (3 H, s, OMe), 2.27 (3 H, s, Me), 2.10 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 156.2 (C), 151.6 (C), 130.7 (CH), 127.6 (CH), 126.7 (CH), 124.9 (CH), 123.6 (C), 123.5 (C), 120.8 (CH), 61.9 (OMe), 15.8 (Me), 10.2 (Me); *m/z* (ESI) 242 (63%), 228 (MNa^+, 10), 206 (MH^+, 100).

2-((1*E*)-3-(Methoxyimino)but-1-enyl)-6-methylphenyl 3-phenylpropiolate 422

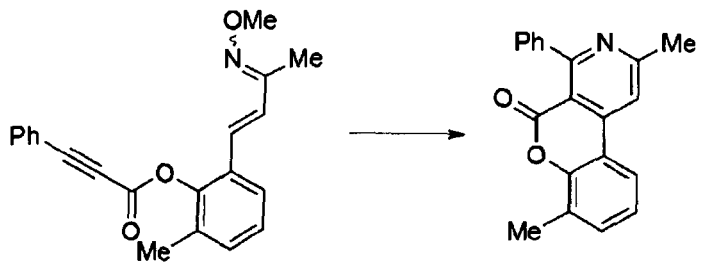


421 **422**

To a solution of phenylpropiolic acid (1.50 g, 9.00 mmol) in dichloromethane (35 mL) was added thionyl chloride (1.97 mL, 27.0 mmol). The reaction mixture was heated to 40 °C for 18 h and then concentrated *in vacuo*. The crude acid chloride was dissolved in dry DMF (6 mL) and added to a suspension of phenol **421** (0.616 g, 3.00 mmol) and potassium carbonate (3.52 g, 25.5 mmol) in dry DMF (6 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Water (75 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 75 mL). The combined organics were washed with water (2 × 75 mL) and saturated brine (75 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:19 to 1:9) to afford the *title compound* as a colourless solid (0.990 g, 99%), mp 103-105 °C (from dichloromethane-hexane); (Found: C, 75.43; H, 5.74; N, 3.93. $C_{21}H_{19}NO_3$ requires C, 75.66; H, 5.74; N, 4.20%); (Found: MH^+, 334.1435. $C_{21}H_{19}NO_3$ + H requires 334.1438); ν_{max} ($CHCl_3$)/cm^{-1} 2235 (C≡C), 1721 (C=O), 1612 (C=C), 1579 (C=C), 1491 (C=C), 1463 (C=C); δ_H (400 MHz; $CDCl_3$) 7.64 (2 H, d, J = 8.0 Hz, ArH), 7.53-7.50 (2 H, m, ArH), 7.42 (2 H, t, J = 8.0 Hz, ArH), 7.21-7.20 (2 H, m, ArH), 6.93 (1 H, d, J = 16.5 Hz, C=CH), 6.85 (1 H, d, J = 16.5 Hz, C=CH), 3.95 (3 H, s, OMe), 2.27 (3 H, s, Me), 2.06 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 164.2 (C), 162.3 (C), 158.8 (C), 151.2 (C), 144.0 (C), 140.9 (C), 133.8 (C), 128.7 (CH), 128.0 (CH),

127.2 (C), 124.0 (CH), 121.2 (CH), 116.0 (C), 113.5 (CH), 111.8 (C), 25.4 (Me), 15.8 (Me); *m/z* (ESI) 356 (MNa^+, 100%), 334 (MH^+, 32).

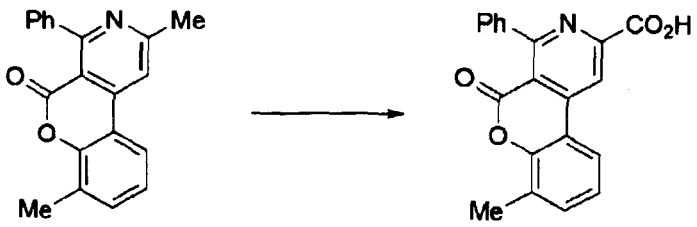
2,7-Dimethyl-4-phenyl-5*H*-chromeno[3,4-c]pyridin-5-one 423



422 **423**

A solution of oxime **422** (1.00 g, 3.00 mmol) in xylene (50 mL) was split into two equal portions and placed in two sealed reaction vessels. The reaction vessels were then heated to 180 °C for 24 h. The two reaction mixtures were then recombined and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9 to 1:4) to afford the *title compound* as a colourless solid (0.434 g, 48%), mp 196-197 °C (from ethyl acetate-hexane); (Found: MH^+, 302.1173. $C_{20}H_{15}NO_2$ + H requires 302.1176); ν_{max} ($CHCl_3$)/cm^{-1} 1742 (C=O), 1615 (C=C), 1592 (C=C), 1579 (C=C), 1551 (C=C), 1497 (C=C); δ_H (400 MHz; $CDCl_3$) 7.94 (1 H, d, J = 8.0 Hz, ArH), 7.80 (1 H, s, ArH), 7.57-7.54 (2 H, m, ArH), 7.49-7.46 (3 H, m, ArH), 7.45 (1 H, d, J = 8.0 Hz, ArH), 7.27 (1 H, t, J = 8.0 Hz, ArH), 2.78 (3 H, s, Me), 2.49 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 164.1 (C), 162.3 (C), 158.8 (C), 151.2 (C), 144.0 (C), 140.9 (C), 133.8 (CH), 128.6 (CH), 128.0 (CH), 127.1 (C), 124.0 (CH), 121.2 (CH), 115.9 (C), 113.5 (CH), 111.7 (C), 25.4 (Me), 15.8 (Me); *m/z* (ESI) 324 (MNa^+, 82%), 302 (MH^+, 100).

7-Methyl-5-oxo-4-phenyl-5*H*-chromeno[3,4-c]pyridine-2-carboxylic acid 424



423 **424**

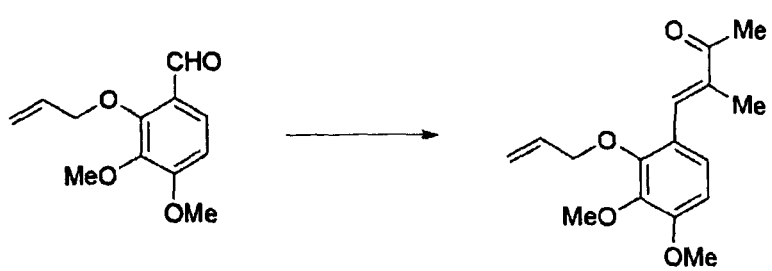
To a solution of **423** (0.405 g, 1.34 mmol) in pyridine (10 mL) was added selenium dioxide (0.597 g, 5.38 mmol). The reaction mixture was heated under reflux for 16 h, cooled to room temperature and filtered through celite. The filter cake was washed with chloroform (20 mL) and the combined organics concentrated *in vacuo*. The crude product was dissolved in ethyl acetate (100 mL), washed with water (100mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a pale orange solid (0.424 g, 95%), mp 222-224 °C (from dichloromethane-hexane); (Found: C, 72.01; H, 4.00; N, 4.09. $C_{20}H_{13}NO_4$ requires C, 72.50; H, 3.95; N, 4.23%); (Found: $[M-H]^-$, 330.0770. $C_{20}H_{13}NO_4$ - H requires 330.0772); ν_{max} ($CHCl_3$)/cm^{-1} 1768 (C=O), 1747 (C=O), 1601 (C=C), 1553 (C=C), 1492 (C=C); δ_H (400 MHz; DMSO) 8.73 (1 H, s, ArH), 8.33 (1 H, d, J = 8.0 Hz, ArH), 7.59-7.55 (3 H, m, ArH), 7.48-7.42 (3 H, m, ArH), 7.33 (1 H, t, J = 8.0 Hz, ArH), 2.37 (3 H, s, Me); δ_C (100 MHz; DMSO) 165.8 (C), 162.7 (C), 157.6 (C), 150.5 (C), 144.5 (C), 140.5 (C), 134.2 (CH), 129.0 (CH), 128.4 (CH), 127.4 (CH), 125.7 (C), 124.3 (CH), 122.5 (CH), 115.7 (C), 115.4 (CH), 15.2 (Me); *m/z* (ESI) 330 ($M-H^-$, 17%), 286 ($[M-CO_2]^-$, 100).

2-(Allyloxy)-3,4-dimethoxybenzaldehyde

279

Following general procedure 6, the *title compound* was obtained from 3,4-dimethoxysalicaldehyde **279** (5.25 g, 28.8 mmol), potassium carbonate (5.97 g, 43.2 mmol) and allyl bromide (12.5 mL, 144 mmol) as a colourless oil (5.62 g, 88%); (Found: MNa^+, 245.0778. $C_{12}H_{14}O_4$ + Na requires 245.0784); ν_{max} ($CHCl_3$)/cm^{-1} 1675 (C=O), 1591 (C=C), 1497 (C=C), 1463 (C=C), 1098 (C-O); δ_H (500 MHz; $CDCl_3$) 10.27 (1 H, s, CHO), 7.59 (1 H, d, J = 8.5 Hz, ArH), 6.75 (1 H, d, J = 8.5 Hz, ArH), 6.07 (1 H, ddt, J = 17.1, 10.3 and 6.0 Hz, CH_2=C<u>H</u>), 5.37 (1 H, ddt, J = 17.1, 1.5 and 1.5 Hz, C<u>H</u>$_2$=CH), 5.28 (1 H, ddt, J = 10.3, 1.5 and 1.5 Hz, C<u>H</u>$_2$=CH), 4.69 (2 H, dt, J = 6.0 and 1.5 Hz, CH_2), 3.92 (3 H, s, OMe), 3.87 (3 H, s, OMe); δ_C (125 MHz; $CDCl_3$) 189.1 (CHO), 159.3 (C), 155.6 (C), 141.8 (C), 133.2 (CH), 124.1 (CH), 123.8 (C), 118.9 (CH_2), 107.6 (CH), 75.4 (CH_2), 61.0 (OMe), 56.2 (OMe); *m/z* (ESI) 467 (21%), 245 (MNa^+, 100%).

(*E*)-4-(2-(Allyloxy)-3,4-dimethoxyphenyl)-3-methylbut-3-en-2-one 426

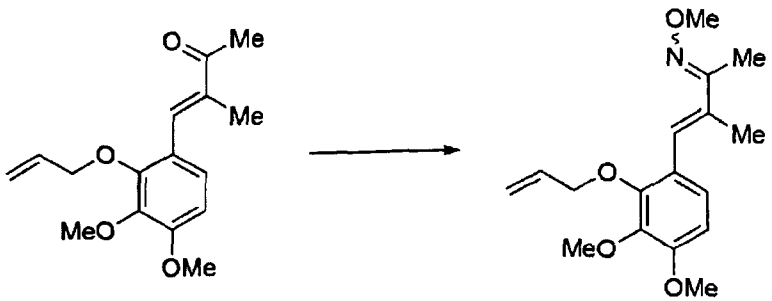


426

Following general procedure 7, the *title compound* was prepared from 2-(allyloxy)-3,4-dimethoxybenzaldehyde (5.00 g, 22.5 mmol), potassium *tert*-butoxide (4.13 g,

33.8 mmol) and diethyl 1-methyl-2-oxopropylphosphonate **319** (7.03 g, 33.8 mmol) as a colourless oil (5.79 g, 93%); (Found: MH^+, 277.1423. $C_{16}H_{20}O_4$ + H requires 277.1434); ν_{max} ($CHCl_3$)/cm^{-1} 1660 (C=O), 1625 (C=C), 1595 (C=C), 1496 (C=C), 1463 (C=C), 1100 (C-O); δ_H (400 MHz; $CDCl_3$) 7.72 (1 H, s, CH), 7.15 (1 H, d, J = 8.5 Hz, ArH), 6.73 (1 H, d, J = 8.5 Hz, ArH), 6.07 (1 H, m, CH_2=C<u>H</u>), 5.40 (1 H, dd, J = 17.0 and 1.5 Hz, C<u>H</u>$_2$=CH), 5.25 (1 H, dd, J = 9.0 and 1.5 Hz, C<u>H</u>$_2$=CH), 4.56 (2 H, m, CH_2), 3.91 (3 H, s, OMe), 3.90 (3 H, s, OMe), 2.45 (3 H, s, Me), 2.01 (3 H, s, Me); δ_C (125 MHz; $CDCl_3$) 200.5 (C), 154.4 (C), 151.5 (C), 142.3 (C), 136.7 (C), 135.5 (CH), 133.9 (CH), 125.0 (CH), 123.2 (C), 117.9 (CH_2), 107.1 (CH), 74.8 (CH_2), 61.0 (OMe), 56.1 (OMe), 25.8 (Me), 13.0 (Me); *m/z* (ESI) 299 (MNa^+, 100%), 277 (12).

(3*E*)-4-(2-(Allyloxy)-3,4-dimethoxyphenyl)-3-methylbut-3-en-2-one *O*-methyl oxime

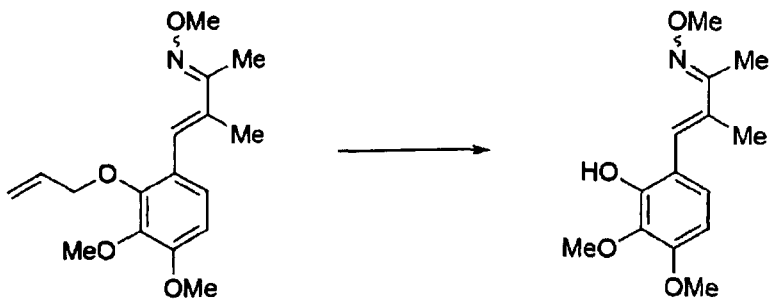


426

Following general procedure 9, the *title compound* was obtained from ketone **426** (5.53 g, 20.0 mmol), methoxylamine hydrochloride (2.09 g, 25.0 mmol) and sodium acetate trihydrate (2.86 g, 21.0 mmol) as a colourless oil (5.85 g, 96%); (Found: MH^+, 306.1691. $C_{17}H_{23}NO_4$ + H requires 306.1700); ν_{max} ($CHCl_3$)/cm^{-1} 1598 (C=C), 1494 (C=C), 1464 (C=C), 1097 (C-O); δ_H (400 MHz; $CDCl_3$) 7.00 (1 H, d, J = 8.8 Hz, ArH), 6.93 (1 H, s, C=CH), 6.69 (1 H, d, J = 8.8 Hz, ArH), 6.10-6.01 (1 H, m, C<u>H</u>=CH$_2$), 5.35 (1 H, ddt, J = 17.2, 1.6 and 1.5 Hz, CH=C<u>H</u>$_2$), 5.20 (1 H, m,

CH=C$\underline{H_2}$), 4.49 (2 H, dt, J = 5.8 and 1.5 Hz, CH_2), 3.95 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.87 (3 H, s, OMe), 2.09 (3 H, s, Me), 2.04 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 157.1 (C), 153.0 (C), 151.0 (C), 142.3 (C), 134.2 (CH), 134.1 (C), 126.0 (CH), 124.9 (CH), 124.6 (C), 117.5 (CH_2), 107.0 (CH), 74.4 (CH_2), 61.8 (OMe), 61.0 (OMe), 56.0 (OMe), 14.4 (Me), 10.7 (Me); *m/z* (ESI) 328 (MNa^+, 100%), 306 (MH^+, 60), 287 (16).

(*E*)-4-(2-Hydroxy-3,4-dimethoxyphenyl)-3-methylbut-3-en-2-one O-methyl oxime 427

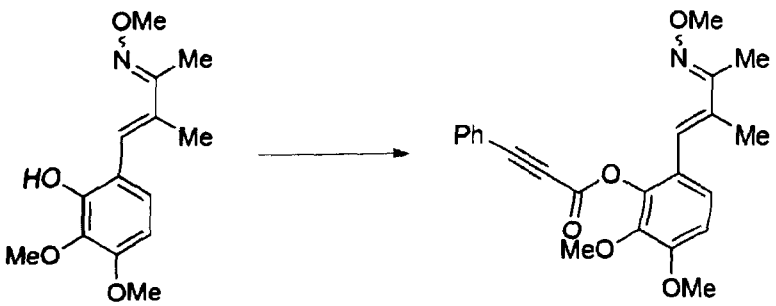


427

To a solution of the oxime (5.75 g, 18.8 mmol), palladium(II) acetate (0.423 g, 1.88 mmol) and triphenylphosphine (7.40 g, 28.2 mmol) in THF (130 mL) was added morpholine (1.97 mL, 22.6 mmol) dropwise over 15 min. The reaction mixture was stirred at room temperature for 14 h. The solvent was removed *in vacuo* and the residue purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9 to 1:4) to afford the *title compound* as a colourless solid (4.00 g, 80%), mp 75-76 °C (from dichloromethane-hexane); (Found: C, 63.24; H, 7.19; N, 5.26. $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28%); (Found: MH^+, 266.1385. $C_{14}H_{19}NO_4$ + H requires 266.1387); ν_{max} ($CHCl_3$)/cm^{-1} 3518 (O-H), 1615 (C=C), 1582 (C=C), 1508 (C=C), 1460 (C=C), 1097 (C-O); δ_H (400 MHz; $CDCl_3$) 6.98 (1 H, d, J = 8.8 Hz, ArH), 6.90 (1 H, s, C=CH), 6.50 (1 H, d, J = 8.8 Hz, ArH), 6.00 (1 H, s, ArOH), 3.95 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.89 (3 H, s, OMe), 2.12 (3 H, s, Me),

2.05 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 157.2 (C), 151.5 (C), 147.5 (C), 135.3 (C), 134.3 (C), 125.1 (CH), 124.7 (CH), 117.5 (C), 103.3 (CH), 61.8 (OMe), 61.0 (OMe), 55.8 (OMe), 14.5 (Me), 10.9 (Me); *m/z* (ESI) 288 (MNa^+, 100%), 266 (MH^+, 40).

2,3-dimethoxy-6-((1*E*)-3-(methoxyimino)-2-methylbut-1-enyl)phenyl 3-phenylpropiolate 428



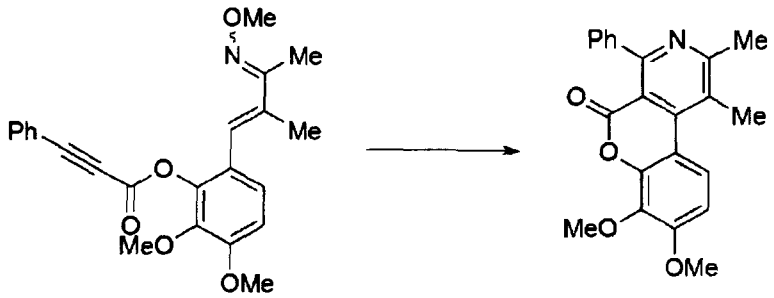
427 **428**

To a solution of phenylpropiolic acid (0.997 g, 6.00 mmol) in dichloromethane (20 mL) was added thionyl chloride (1.31 mL, 18.0 mmol). The reaction mixture was heated to 40 °C for 18 h and then concentrated *in vacuo*. The crude acid chloride was dissolved in dry DMF (5 mL) and added to a suspension of phenol **427** (0.531 g, 2.00 mmol) and potassium carbonate (2.35 g, 17.0 mmol) in dry DMF (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Water (75 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 75 mL). The combined organics were washed with water (2 × 75 mL) and saturated brine (75 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:19 to 1:9) to afford the *title compound* as a colourless solid (0.708 g, 90%), mp 138-139 °C (from ethyl acetate-hexane); (Found: C, 69.43; H, 5.90; N, 3.47. $C_{23}H_{23}NO_5$ requires C, 70.21; H, 5.89; N, 3.56%); (Found: MH^+, 394.1636. $C_{23}H_{24}NO_5$ + H requires 394.1649); ν_{max} ($CHCl_3$)/cm^{-1} 2226 (C≡C), 1727 (C=O),

1608 (C=C), 1577 (C=C), 1500 (C=C), 1463 (C=C), 1086 (C-O); δ_H (400 MHz; $CDCl_3$) 7.62 (2 H, d, J = 7.2 Hz, ArH), 7.47 (1 H, t, J = 7.2 Hz, ArH), 7.40 (2 H, t, J = 7.2 Hz, ArH), 7.05 (1 H, d, J = 8.6 Hz, ArH), 6.88 (1 H, d, J = 8.6 Hz, ArH), 3.94 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.91 (3 H, s, OMe), 2.08 (3 H, s, Me), 2.02 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 156.6 (C), 152.8 (C), 151.7 (C), 141.8 (C), 141.3 (C), 136.7 (C), 133.3 (CH), 131.1 (CH), 128.7 (CH), 127.4 (C), 124.8 (CH), 123.9 (CH), 119.3 (C), 110.1 (CH), 88.8 (C≡C), 79.9 (C≡C), 61.9 (OMe), 61.0 (OMe), 56.2 (OMe), 14.4 (Me), 10.8 (Me); *m/z* (ESI) 452 (26%), 416 (MNa^+, 100), 394 (MH^+, 25).

To a solution of phenol **427** (0.531 g, 2.00 mmol) and DMAP (0.489 g, 4.00 mmol) in THF (4 mL) at 0 °C was added the acid chloride in THF (4 mL) dropwise over 15 min. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. Water (50 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (50 mL) and saturated brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:19) to afford the title compound as a colourless solid (0.663 g, 85%); data as above.

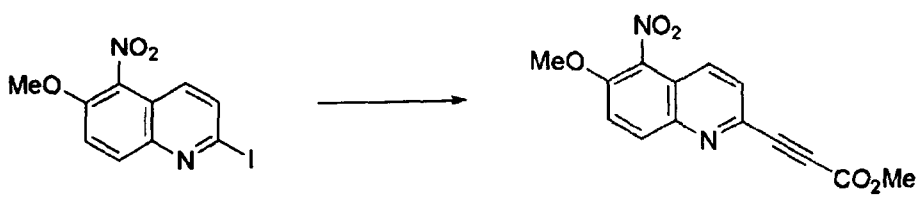
7,8-Dimethoxy-1,2-dimethyl-4-phenyl-5*H*-chromeno[3,4-c]pyridin-5-one 429



428 **429**

Following general procedure 11, the *title compound* was obtained from oxime **428** (0.500 g, 1.27 mmol) after 24 h at 180 °C as a colourless solid (0.212 g, 46%), mp 175-177 °C (from dichloromethane-hexane); (Found: MH^+, 362.1378. $C_{22}H_{19}NO_4$ + H requires 362.1387); ν_{max} ($CHCl_3$)/cm^{-1} 1742 (C=O), 1610 (C=C), 1544 (C=C), 1511 (C=C); δ_H (400 MHz; $CDCl_3$) 7.89 (1 H, d, J = 9.2 Hz, ArH), 7.54-7.51 (2 H, m, ArH), 7.46-7.42 (3 H, m, ArH), 6.92 (1 H, d, J = 9.2 Hz, ArH), 3.99 (3 H, s, OMe), 3.98 (3 H, s, OMe), 2.76 (3 H, s, Me), 2.74 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 162.3 (C), 160.7 (C), 159.0 (C), 154.8 (C), 146.9 (C), 142.8 (C), 141.4 (C), 136.5 (C), 128.7 (CH), 128.4 (CH), 128.0 (CH), 124.5 (C), 123.7 (CH), 112.3 (C), 107.3 (CH), 61.6 (OMe), 56.3 (OMe), 24.9 (Me), 19.3 (Me); *m/z* (ESI) 384 (MNa^+, 55%), 362 (MH^+, 100%).

Methyl 3-(6-methoxy-5-nitroquinolin-2-yl)propiolate 430

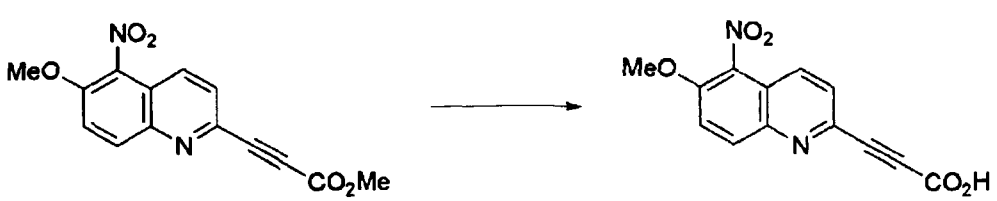


317 **430**

To a solution of 2-iodo-6-methoxy-5-nitroquinoline **317** (2.00 g, 6.06 mmol), bis(triphenylphosphine)palladium(II) chloride (0.304 g, 0.433 mmol) and copper(I)

iodide (0.346 g, 1.82 mmol) in THF (40 mL) was added methyl propiolate (1.35 mL, 15.2 mmol) and diisopropylethylamine (1.58 mL, 9.09 mmol). The reaction mixture was heated to 50 °C for 3 h, then cooled to room temperature and partitioned between saturated ammonium chloride (200 mL) and ethyl acetate (3 × 200 mL). The combined organics were washed with saturated ammonium chloride (200 mL) and saturated brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the *title compound* as a colourless solid (1.60 g, 92%), mp 209-211 °C (from dichloromethane-hexane); (Found: C, 58.43; H, 3.46; N 9.56. $C_{14}H_{10}N_2O_5$ requires C, 58.74; H, 3.52; N, 9.79%); (Found: MH^+, 287.0660. $C_{14}H_{10}N_2O_5$ + H requires 287.0662); ν_{max} ($CHCl_3$)/cm^{-1} 2230 (C≡C), 1717 (C=O), 1628 (C=C), 1593 (C=C), 1533 (C=C), 1498 (C=C), 1347 (N=O), 1079 (C-O); δ_H (400 MHz; $CDCl_3$) 8.60 (1 H, d, J = 9.2 Hz, ArH), 8.11 (1 H, d, J = 8.8 Hz, ArH), 7.72 (1 H, d, J = 8.8 Hz, ArH), 7.67 (1 H, d, J = 9.2 Hz, ArH), 4.12 (3 H, s, OMe), 3.89 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 153.9 (C), 150.6 (C), 142.0 (C), 139.7 (C), 134.4 (CH), 129.9 (CH), 126.8 (CH), 121.0 (C), 117.4 (CH), 83.6 (C≡C), 79.7 (C≡C), 57.3 (OMe), 53.2 (OMe); *m/z* (ESI) 309 (MNa^+, 76%), 287 (MH^+, 100).

3-(6-Methoxy-5-nitroquinolin-2-yl)propiolic acid 431



430 **431**

To a solution of methyl ester **430** (0.500 g, 1.75 mmol) in THF (30 mL) was added lithium hydroxide monohydrate (0.376 g, 8.75 mmol) in water (6 mL). The reaction

mixture was stirred at room temperature for 3 h, acidified with hydrochloric acid (2 M) and extracted into ethyl acetate (3 × 50 mL). The combined organics were washed with water (2 × 50 mL) and saturated brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a pale yellow solid (0.467 g, 98%), mp 220-224 °C with decomp. (from ethyl acetate-hexane); (Found: MH^+, 273.0280. $C_{13}H_8N_2O_5$ + H requires 273.0506); ν_{max} ($CHCl_3$)/cm^{-1} 2220 (C≡C), 1725 (C=O), 1623 (C=C), 1588 (C=C), 1515 (C=C), 1493 (C=C), 1356 (N=O), 1076 (C-O); δ_H (400 MHz; $CDCl_3$) 8.35 (1 H, d, J = 9.6 Hz, ArH), 8.21 (1 H, d, J = 8.8 Hz, ArH), 8.05 (1 H, d, J = 9.6 Hz, ArH), 7.91 (1 H, d, J = 8.8 Hz, ArH), 4.12 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 153.7 (C), 150.2 (C), 141.5 (C), 139.1 (C), 134.1 (CH), 133.3 (C), 129.9 (CH), 127.1 (CH), 120.0 (C), 118.9 (CH), 82.1 (C≡C), 80.7 (C≡C), 57.6 (OMe); *m/z* (ESI) 273 (MH^+, 100%), 242 (74).

5-Amino-2-iodo-6-methoxyquinoline 434

317 **434**

To a suspension of **317** (1.65 g, 5.00 mmol) and iron powder (1.50 g) in ethanol (30 mL) was added glacial acetic acid (2.00 mL, 35.0 mmol). The reaction mixture was heated under reflux for 4 h, then cooled to room temperature and partitioned between water (100 mL) and chloroform (3 × 100 mL). The combined organics were washed with water (2 × 100 mL) and saturated brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* (1.41 g, 94%). The crude product was used without further purification, mp 138-140 °C (ethyl acetate-hexane); (Found: C, 40.20; H, 3.02; N 9.34. $C_{10}H_9IN_2O$ requires C, 40.02; H, 3.02; N, 9.33%); (Found:

MH^+, 300.9824. $C_{10}H_9IN_2O$ + H requires 300.9832); ν_{max} ($CHCl_3$)/cm^{-1} 3477 (NH), 3392 (NH), 1616 (C=C), 1609 (C=C), 1570 (C=C), 1561 (NH), 1499 (C=C), 1465 (C=C); δ_H (400 MHz; $CDCl_3$) 7.5 (1 H, d, J = 8.8 Hz, ArH), 7.57 (1 H, d, J = 8.8 Hz, ArH), 7.50 (1 H, d, J = 9.2 Hz, ArH), 7.37 (1 H, d, J = 9.2 Hz, ArH), 4.27 (2 H, br s, NH_2), 3.97 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 145.3 (C), 143.1 (C), 130.4 (CH), 130.0 (CH), 129.9 (C), 118.9 (CH), 117.4 (C), 116.6 (CH), 116.2 (C), 56.5 (OMe); *m/z* (ESI) 322 (MNa^+, 4%), 300 (MH^+, 100%).

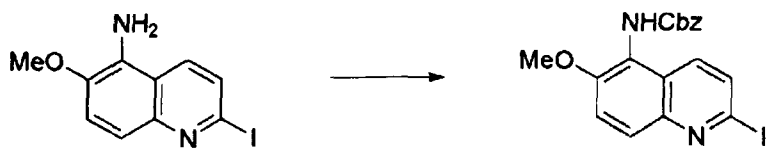
2-Iodo-6-methoxyquinoline-5,8-dione 435

434 **435**

To a solution of 5-amino-2-iodo-6-methoxyquinoline **434** (1.00 g, 3.33 mmol) in acetone (125 mL) was added Fremy's salt (3.58 g, 13.3 mmol) in sodium dihydrogenphosphate buffer solution (0.3 M in H_2O; 125 mL) over 5 min. The reaction mixture was stirred at room temperature for 12 h and the acetone removed *in vacuo*. The resulting aqueous residue was extracted with dichloromethane (3 × 100 mL) and the combined organics washed with saturated brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ether-dichloromethane (0:1 to 1:49) to afford the *title compound* as a pale yellow solid (0.930 g, 89%), mp 241-243 °C (from dichloromethane-hexane); (Found: C, 38.33; H, 1.79; N, 4.13. $C_{10}H_6INO_3$ requires C, 38.12; H, 1.92; N, 4.45%); (Found: MH^+, 315.9464. $C_{10}H_6INO_3$ + H requires 315.9465); ν_{max} ($CHCl_3$)/cm^{-1} 1690 (C=O), 1667 (C=O), 1609 (C=C), 1564 (C=C),

1499 (C=C), 1096 (C-O); δ_H (400 MHz; $CDCl_3$) 8.12 (1 H, d, J = 8.0 Hz, ArH), 8.02 (1 H, d, J = 8.0 Hz, ArH), 6.34 (1 H, s, ArH), 3.95 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 181.5 (C), 179.4 (C), 160.0 (C), 147.8 (C), 139.2 (CH), 135.3 (CH), 127.1 (C), 125.9 (C), 110.3 (CH), 56.8 (OMe); *m/z* (ESI) 337 (MNa^+, 100%), 315 (MH^+, 21).

Benzyl 2-iodo-6-methoxyquinolin-5-ylcarbamate 436

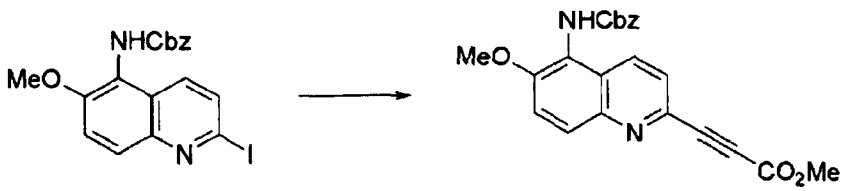


434 **436**

To a solution of aminoquinoline **434** (0.300 g, 1.00 mmol) in THF (5 mL) was added benzyl chloroformate (0.214 mL, 1.50 mmol) and diisopropylethylamine (0.348 mL, 2.00 mmol). The reaction mixture was stirred at room temperature for 16 h, diluted with water (25 mL) and extracted into dichloromethane (3 × 25 mL). The combined organic extracts were washed with water (25 mL) and saturated brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (2:3) to afford the *title compound* as a colourless solid (0.397 g, 91%), mp 204-205 °C (from dichloromethane-hexane); (Found: C, 49.95; H, 3.48; N 6.49. $C_{18}H_{15}IN_2O_3$ requires C, 49.79; H, 3.48; N, 6.45%); (Found: MH^+, 435.0197. $C_{18}H_{15}IN_2O_3$ + H requires 435.0200); ν_{max} ($CHCl_3$)/cm^{-1} 3414 (NH), 1733 (C=O), 1619 (C=C), 1581 (C=C), 1560 (NH), 1506 (C=C), 1483 (C=C); δ_H (400 MHz; $CDCl_3$) 7.98 (1 H, d, J = 9.3 Hz, ArH), 7.79 (1 H, d, J = 8.8 Hz, ArH), 7.65 (1 H, d, J = 8.8 Hz, ArH), 7.45 (1 H, d, J = 9.3 Hz, ArH), 7.42-7.34 (5 H, m, ArH), 6.63 (1 H, br s, NH), 5.22 (2 H, s, CH_2), 3.95 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 155.3 (C), 151.5 (C), 144.8 (C), 136.0 (C), 133.0 (CH), 132.0 (CH), 128.9 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 125.1 (C), 118.9

(C), 116.5 (C), 116.2 (CH), 67.6 (CH_2), 56.4 (OMe); *m/z* (ESI) 457 (MNa^+, 100%), 435 (MH^+, 53).

3-(5-(Benzyloxycarbonylamino)-6-methoxyquinolin-2-yl)propiolic acid methyl ester 437

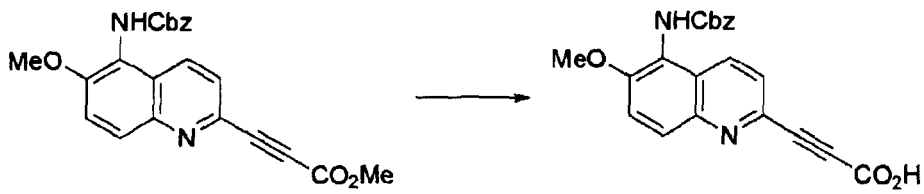


436 **437**

To a solution of iodoquinoline **436** (0.250 g, 0.576 mmol), bis(triphenylphosphine)palladium(II) chloride (0.029 g, 0.041 mmol) and copper(I) iodide (0.033 g, 0.173 mmol) in THF (10 mL) was added methyl propiolate (0.128 mL, 1.44 mmol) and diisopropylethylamine (0.151 mL, 0.864 mmol). The reaction mixture was stirred at 50 °C for 3 h, cooled to room temperature and partitioned between water (25 mL) and ethyl acetate (3 × 25 mL). The combined organics were washed with water (25 mL) and saturated brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the *title compound* as a colourless solid (0.198 g, 88%), mp 194-196 °C (from dichloromethane-hexane); (Found: C, 67.13; H, 4.60; N, 6.95. $C_{22}H_{18}N_2O_5$ requires C, 67.69; H, 4.65; N, 7.18%); (Found: MH^+, 391.1282. $C_{22}H_{18}N_2O_5$ + H requires 391.1288); ν_{max} ($CHCl_3$)/cm^{-1} 3414 (NH), 2229 (C≡C), 1715 (C=O), 1619 (C=C), 1593 (C=C), 1557 (NH), 1501 (C=C), 1463 (C=C); δ_H (400 MHz; $CDCl_3$) 8.22 (1 H, d, J = 8.8 Hz, ArH), 8.09 (1 H, d, J = 9.4 Hz, ArH), 7.57 (1 H, d, J = 8.8 Hz, ArH), 7.55 (1 H, d, J = 9.4 Hz, ArH), 7.45-7.32 (5 H, m, ArH), 6.60 (1 H, br s, NH), 5.23 (2 H, s, CH_2), 3.98 (3 H, s, OMe), 3.87 (3 H,

s, OMe); δ_C (100 MHz; $CDCl_3$) 155.3 (C), 154.0 (C), 143.6 (C), 138.3 (C), 136.0 (C), 132.2 (CH), 130.1 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 124.6 (CH), 118.3 (C), 116.7 (CH), 84.8 (C≡C), 78.8 (C≡C), 67.7 (CH_2), 56.4 (OMe), 53.0 (OMe); *m/z* (ESI) 413 (MNa^+, 100%), 391 (MH^+, 77), 312 (53).

3-(5-(Benzyloxycarbonylamino)-6-methoxyquinolin-2-yl)propiolic acid 438



437 **438**

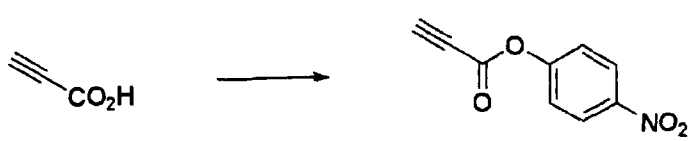
To a solution of propiolate ester **437** (0.150 g, 0.384 mmol) in THF (10 mL) and water (2 mL) was added lithium hydroxide monohydrate (0.081 g, 1.92 mmol). The reaction mixture was stirred at room temperature for 1 h and acidified with hydrochloric acid (2 M). The aqueous phase was extracted with ethyl acetate (3 × 20 mL) and the combined organics washed with water (20 mL) and saturated brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a colourless solid (0.145 g, 100%), mp 147-149 °C (from dichloromethane-hexane); (Found: MNa^+, 399.0953. $C_{21}H_{16}N_2O_5$ + Na requires 399.0957); ν_{max} ($CHCl_3$)/cm^{-1} 3415 (NH), 3289 (OH), 2223 (C≡C), 1702 (C=O), 1613 (C=C), 1550 (NH), 1498 (C=C); δ_H (400 MHz; DMSO) 9.16 (1 H, br s, NH), 8.26 (1 H, d, J = 8.8 Hz, ArH), 8.04 (1 H, d, J = 9.4 Hz, ArH), 7.85 (1 H, d, J = 9.4 Hz, ArH), 7.74 (1 H, d, J = 8.8 Hz, ArH), 7.46-7.36 (5 H, m, ArH), 5.13 (2 H, s, CH_2), 3.95 (3 H, s, OMe); δ_C (100 MHz; DMSO) 154.9 (C), 153.9 (C), 143.0 (C), 137.6 (C), 136.8 (C), 131.9 (CH), 129.2 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 126.3 (C), 124.7 (CH), 118.7 (C), 118.6 (CH), 83.0 (C≡C), 80.0 (C≡C), 65.9 (CH_2), 56.5 (OMe); *m/z* (ESI) 399 (MNa^+, 12%), 331 (M-CO_2H, 100).

1-(1H-1,2,3-Benzotriazol-1-yl)-2-propyn-1-one[196] 440

446 **440**

To a solution of benzotriazole (4.76 g, 40.0 mmol) in dichloromethane (50 mL) was added thionyl chloride (0.73 mL, 10.0 mmol). The reaction mixture was stirred at room temperature for 30 min and propiolic acid **446** (0.62 mL, 10.0 mmol) was added. The reaction was stirred for a further 2 h, the colourless solid was filtered off and washed with dichloromethane (2 × 50 mL). The combined organics were washed with saturated sodium hydrogen carbonate (2 × 50 mL) and saturated brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the title compound as a colourless solid (0.800 g, 47%), mp 105-106 °C (from dichloromethane-hexane) (lit., 99 °C); δ_H (400 MHz; $CDCl_3$) 8.18 (1 H, d, J = 8.4 Hz, ArH), 8.11 (1 H, d, J = 8.0 Hz, ArH), 7.66 (1 H, td, J = 8.4 and 1.2 Hz, ArH), 7.52 (1 H, td, J = 8.0 and 1.2 Hz, ArH), 3.77 (1 H, s, C≡CH); δ_C (100 MHz; $CDCl_3$) 149.2 (C), 146.2 (C), 130.9 (CH), 130.6 (C), 126.9 (CH), 120.5 (CH), 114.2 (CH), 84.2 (C≡CH), 74.5 (C≡CH).

4-Nitrophenyl propiolate[207] 442

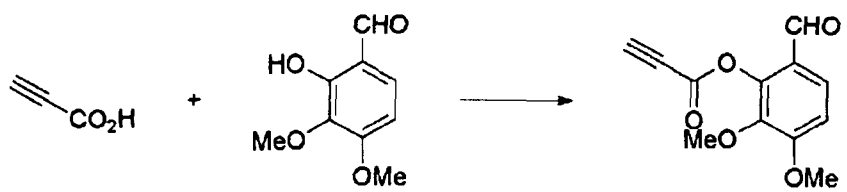


446 **442**

To a solution of propiolic acid **446** (0.246 mL, 4.00 mmol), 4-nitrophenol (0.556 g, 4.00 mmol) and DMAP (0.024 g, 0.200 mmol) in dichloromethane (15 mL) at 0 °C was added DCC (1 M in dichloromethane; 5.00 mL, 5.00 mmol) dropwise over 5 min.

The reaction mixture was allowed to warm to room temperature, stirred for 2 h and filtered. The solid was washed with dichloromethane (15 mL), and the combined filtrate concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the title compound as a colourless solid (0.497 g, 65%), mp 135-136 °C (from dichloromethane-hexane) (lit., 132 °C); δ_H (400 MHz; $CDCl_3$) 8.31 (2 H, d, J = 9.2 Hz, ArH), 7.37 (2 H, d, J = 9.2 Hz, ArH), 3.19 (1 H, s, C≡CH); δ_C (100 MHz; $CDCl_3$) 154.2 (C), 149.7 (C), 145.9 (C), 125.4 (CH), 122.3 (CH), 78.1 (C≡CH), 73.6 (C≡CH).

6-Formyl-2,3-dimethoxyphenyl propiolate 447

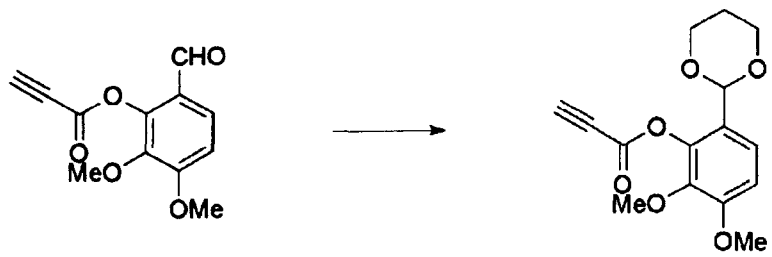


446 **279** **447**

To a solution of propiolic acid **446** (3.69 mL, 60.0 mmol), 2-hydroxy-3,4-dimethoxybenzaldehyde **279** (5.47 g, 30.0 mmol) and DMAP (0.367 g, 3.00 mmol) in dichloromethane (50 mL) at 0 °C was added DCC (1 M in dichloromethane; 60.0 mL, 60.0 mmol) dropwise over 45 min. The reaction mixture was allowed to warm to room temperature, stirred for 17 h and filtered. The solid was washed with dichloromethane (3 × 75 mL) and the combined filtrate concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the *title compound* as a colourless solid (5.76 g, 82%), mp 85-86 °C (from ethyl acetate-hexane); (Found: C, 61.40; H, 4.45. $C_{12}H_{10}O_5$ requires C, 61.54; H, 4.30 %); (Found: MH^+, 235.0603. $C_{12}H_{10}O_5$ + H requires 235.0601); ν_{max} ($CHCl_3$)/cm^{-1} 3298 (alkyne C-H), 2130 (C≡C), 1742 (C=O), 1694 (C=O), 1601 (C=C),

1577 (C=C), 1503 (C=C); δ_H (400 MHz; $CDCl_3$) 9.92 (1 H, s, CHO), 7.58 (1 H, d, J = 8.8 Hz, ArH), 6.94 (1 H, d, J = 8.8 Hz, ArH), 3.93 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.25 (1 H, s, C≡CH); δ_C (100 MHz; $CDCl_3$) 187.3 (C), 158.8 (C), 150.1 (C), 143.9 (C), 141.1 (C), 127.2 (CH), 122.0 (C), 110.2 (CH), 78.1 (C≡CH), 73.6 (C≡CH), 61.0 (OMe), 56.4 (OMe); *m/z* (ESI) 257 (MNa^+, 100%), 235 (MH^+, 51), 207 (58), 183 (47).

6-(1,3-Dioxan-2-yl)-2,3-dimethoxyphenyl propiolate 448

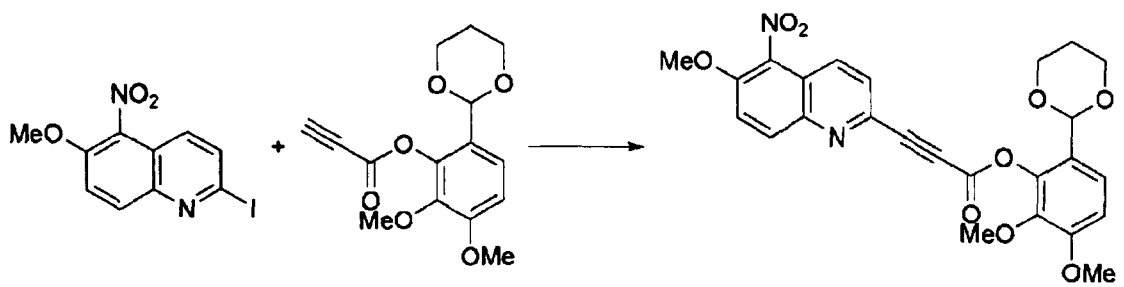


447 **448**

To a solution of 6-formyl-2,3-dimethoxyphenyl propiolate **447** (2.81 g, 12.0 mmol) and *para*-toluenesulfonic acid (0.060 g) in toluene (180 mL) was added 1,3-propanediol (4.34 mL, 60.0 mmol). The reaction mixture was heated under reflux under Dean-Stark apparatus for 22 h, then cooled to room temperature and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:4) to afford the *title compound* as a colourless solid (2.11 g, 60%), mp 65-66 °C (from ethyl acetate-hexane); (Found: C, 61.49; H, 5.49. $C_{15}H_{16}O_6$ requires C, 61.64; H, 5.52%); (Found: MH^+, 293.1001. $C_{15}H_{16}O_6$ + H requires 293.1020); ν_{max} ($CHCl_3$)/cm^{-1} 3299 (alkyne C-H), 2128 (C≡C), 1740 (C=O), 1616 (C=C), 1506 (C=C), 1464 (C=C), 1086 (C-O); δ_H (400 MHz; $CDCl_3$) 7.32 (1 H, d, J = 8.8 Hz, ArH), 6.86 (1 H, d, J = 8.8 Hz, ArH), 5.54 (1 H, s, CH), 4.27-4.23 (1 H, m, CH_2), 3.96 (2 H, td, J = 12.4 and 2.4 Hz, CH_2), 3.89 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.07 (1 H, s, C≡CH), 2.27-2.17 (1 H, m CH), 1.45-1.41 (1

H, m, CH); δ_C (100 MHz; $CDCl_3$) 153.9 (C), 150.3 (C), 141.1 (C), 140.9 (C), 124.0 (C), 121.6 (CH), 110.3 (CH), 97.9 (CH), 74.1 (C≡CH), 67.4 (CH_2), 60.8 (OMe), 56.1 (OMe), 25.6 (CH_2); *m/z* (ESI) 315 (MNa^+, 100%), 293 (MH^+, 39).

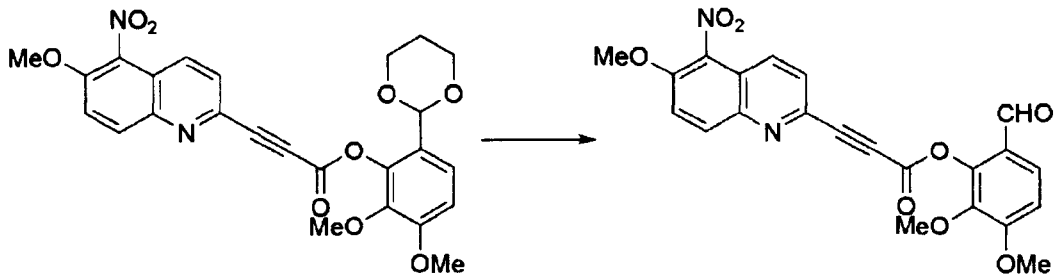
6-(1,3-Dioxan-2-yl)-2,3-dimethoxyphenyl 3-(6-methoxy-5-nitroquinolin-2-yl)propiolate 449



317 **448** **449**

Following general procedure 8, the *title compound* was obtained from 2-iodo-6-methoxy-5-nitroquinoline **317** (0.975 g, 2.95 mmol) and 6-(1,3-dioxan-2-yl)-2,3-dimethoxyphenyl propiolate **448** (1.29 g, 4.43 mmol) as a colourless solid (0.438 g, 30%), mp 201-202 °C (from ethyl acetate-hexane); (Found: MH^+, 495.1398. $C_{25}H_{22}N_2O_9$ + H requires 495.1398); ν_{max} ($CHCl_3$)/cm^{-1} 2229 (C≡C), 1737 (C=O), 1628 (C=C), 1593 (C=C), 1533 (C=C), 1496 (C=C), 1463 (C=C), 1347 (N=O), 1084 (C-O); δ_H (400 MHz; $CDCl_3$) 8.34 (1 H, d, J = 9.6 Hz, ArH), 8.15 (1 H, d, J = 8.8 Hz, ArH), 7.80 (1 H, d, J = 8.8 Hz, ArH), 7.69 (1 H, d, J = 9.6 Hz, ArH), 7.36 (1 H, d, J = 8.8 Hz, ArH), 6.88 (1 H, d, J = 8.8 Hz, ArH), 5.61 (1 H, s, CH), 4.29-4.15 (2 H, m, CH_2), 4.13 (3 H, s, OMe), 4.00 (2 H, td, J = 12.0 and 2.0 Hz, CH_2), 3.91 (3 H, s, OMe), 3.90 (3 H, s, OMe), 2.30-2.18 (1 H, m, CH), 1.45-1.42 (1 H, m, CH); δ_C (100 MHz; $CDCl_3$) 153.9 (C=O), 134.5 (CH), 129.9 (CH), 127.1 (CH), 124.1 (C), 121.6 (CH), 117.4 (CH), 110.4 (CH), 97.7 (CH), 67.5 (CH_2), 60.9 (OMe), 57.3 (OMe), 56.1 (OMe), 25.7 (Me); *m/z* (ESI) 517 (MNa^+, 100%), 495 (MH^+, 37), 388 (24), 312 (27).

6-Formyl-2,3-dimethoxyphenyl 3-(6-methoxy-5-nitroquinolin-2-yl)propiolate 450

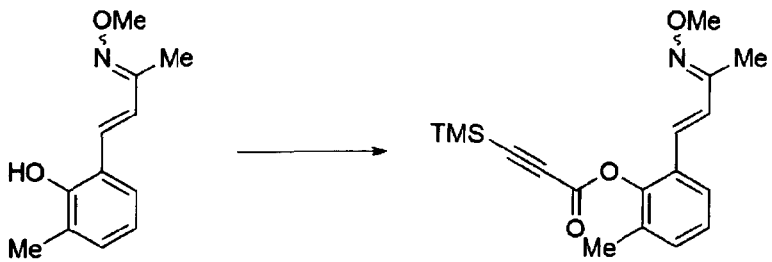


449 **450**

A solution of acetal **449** (0.225 g, 0.455 mmol) in glacial acetic acid (5 mL) and water (0.5 mL) was heated at 50 °C for 3 h, cooled to room temperature and poured into saturated sodium hydrogen carbonate (100 mL). The aqueous phase was extracted with ethyl acetate (3 × 100 mL) and the combined organics washed with saturated sodium hydrogen carbonate (100 mL) and water (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a colourless solid (0.199 g, 100%) which was used without further purification, mp 179-180 °C (from ethyl acetate-hexane); (Found: MH^+, 437.0981. $C_{22}H_{16}N_2O_8$ + H requires 437.0979); ν_{max} ($CHCl_3$)/cm^{-1} 2228 (C≡C), 1738 (C=O), 1694 (C=O), 1628 (C=C), 1600 (C=C), 1578 (C=C), 1533 (C=C), 1501 (C=C), 1461 (C=C), 1346 (N=O), 1082 (C-O); δ_H (400 MHz; $CDCl_3$) 10.06 (1 H, s, CHO), 8.34 (1 H, d, J = 9.6 Hz, ArH), 8.17 (1 H, d, J = 8.8 Hz, ArH), 7.84 (1 H, d, J = 8.8 Hz, ArH), 7.69 (1 H, d, J = 9.6 Hz, ArH), 7.68 (1 H, d, J = 8.8 Hz, ArH), 7.50 (1 H, d, J = 8.8 Hz, ArH), 4.13 (3 H, s, OMe), 4.00 (3 H, s, OMe), 3.93 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 187.2 (C), 158.8 (C), 150.8 (C), 150.6 (C), 144.2 (C), 142.3 (C), 141.2 (C), 139.2 (C), 134.5 (CH), 129.9 (CH), 127.0 (CH), 126.8 (CH), 122.2 (C), 121.2 (C), 117.6 (CH), 110.2 (CH), 86.0 (C≡C), 78.7 (C≡C), 61.1 (OMe), 57.3 (OMe), 56.4 (OMe); *m/z* (ESI) 459 (MNa^+. 100%), 437 (24), 312 (65).

2-((1*E*)-3-(Methoxyimino)but-1-enyl)-6-methylphenyl 3-(trimethylsilyl)propiolate

454



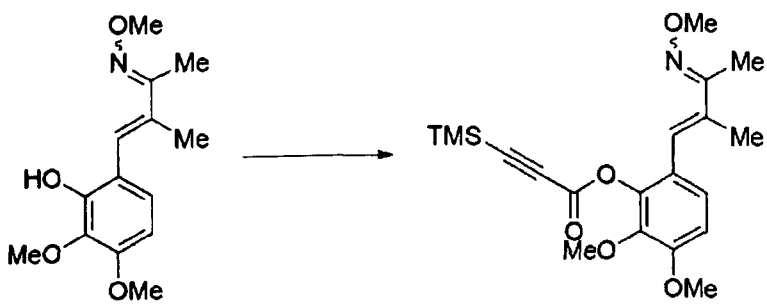
421 **454**

To a solution of 3-(trimethylsilyl)propiolic acid (0.711 g, 5.00 mmol) in freshly distilled oxalyl chloride (0.47 mL, 5.50 mmol) was added DMF (15.0 μL, 0.200 mmol). Vigorous bubbling was observed. The reaction mixture was stirred for 30 min, and the crude product distilled under reduced pressure to give 3-(trimethylsilyl)propiolic acid chloride (bp 62 °C at 20 mm Hg) which was used without further purification.

To a solution of phenol **421** (0.411 g, 2.00 mmol) in THF (4 mL) at 0 °C was added DMAP (0.489 g, 4.00 mmol) in one portion, followed by the acid chloride in THF (4 mL) dropwise over 10 min. The reaction mixture was allowed to warm to room temperature, strirred for 18 h and partitioned between water (50 mL) and ethyl acetate (3 × 50 mL). The combined organics were washed with water (50 mL) and saturated brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the *title compound* as a colourless solid (0.743 g, 92%), mp 68-70 °C (from dichloromethane-hexane); (Found: MH^+, 334.1435. $C_{21}H_{19}NO_3$ + H requires 334.1438); ν_{max} ($CHCl_3$)/cm^{-1} 2181 (C≡C), 1625 (C=C), 1586 (C=C), 1462 (C=C); δ_H (400 MHz; $CDCl_3$) 7.64 (2 H, d, J = 8.0 Hz, ArH), 7.53-7.50 (2 H, m,

ArH), 7.42 (2 H, t, J = 8.0 Hz, ArH), 7.21-7.20 (2 H, m, ArH), 6.93 (1 H, d, J = 16.5 Hz, C=CH), 6.85 (1 H, d, J = 16.5 Hz, C=CH), 3.95 (3 H, s, OMe), 2.27 (3 H, s, Me), 2.06 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 164.2 (C), 162.3 (C), 158.8 (C), 151.2 (C), 144.0 (C), 140.9 (C), 133.8 (C), 128.7 (CH), 128.0 (CH), 127.2 (C), 124.0 (CH), 121.2 (CH), 116.0 (C), 113.5 (CH), 111.8 (C), 25.4 (Me), 15.8 (Me); *m/z* (ESI) 356 (MNa^+, 100%), 334 (MH^+, 32).

2,3-dimethoxy-6-((1*E*)-3-(methoxyimino)-2-methylbut-1-enyl)phenyl 3-(trimethylsilyl)propiolate 455



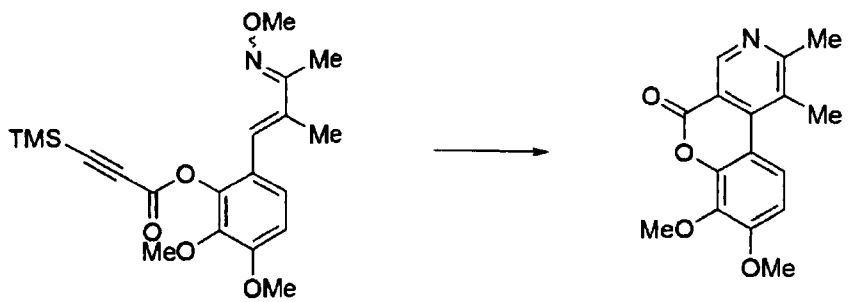
427 **455**

To a solution of 3-(trimethylsilyl)propiolic acid (0.711 g, 5.00 mmol) in freshly distilled oxalyl chloride (0.47 mL, 5.50 mmol) was added DMF (15.0 μL, 0.200 mmol). Vigorous bubbling was observed. The reaction mixture was stirred for 30 min, and the crude product distilled under reduced pressure to give 3-(trimethylsilyl)propiolic acid chloride (bp 62 °C at 20 mm Hg) which was used without further purification.

To a solution of phenol **427** (0.531 g, 2.00 mmol) in THF (4 mL) at 0 °C was added DMAP (0.489 g, 4.00 mmol) in one portion, followed by the acid chloride in THF (4 mL) dropwise over 10 min. The reaction mixture was allowed to warm to room temperature, strirred for 18 h and partitioned between water (50 mL) and ethyl acetate

(3 × 50 mL). The combined organics were washed with water (50 mL) and saturated brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate-light petroleum (1:9) to afford the *title compound* as a pale yellow solid (0.663 g, 85%), mp 76-77 °C (from dichloromethane-hexane); (Found: MH^+, 390.1708. $C_{20}H_{27}NO_5Si$ + H requires 390.1731); ν_{max} ($CHCl_3$)/cm^{-1} 2180 (C≡C), 1728 (C=O), 1607 (C=C), 1501 (C=C), 1086 (C-O); δ_H (400 MHz; $CDCl_3$) 7.02 (1 H, d, J = 8.6 Hz, ArH), 6.84 (1 H, d, J = 8.6 Hz, ArH), 6.63 (1 H, s, C=CH), 3.95 (3 H, s, OMe), 3.89 (3 H, s, OMe), 3.87 (3 H, s, OMe), 2.08 (3 H, s, Me), 1.99 (3 H, s, Me), 0.27 (9 H, s, $SiMe_3$); δ_C (100 MHz; $CDCl_3$) 157.5 (C), 153.6 (C), 151.6 (C), 142.6 (C), 142.2 (C), 137.6 (C), 125.6 (CH), 124.7 (CH), 124.6 (C), 110.9 (CH), 97.9 (C≡C), 94.5 (C≡C), 62.8 (OMe), 61.8 (OMe), 57.0 (OMe), 15.3 (Me), 11.7 (Me), 0.0 ($SiMe_3$); *m/z* (ESI) 412 (MNa^+, 100%), 390 (MH^+, 56), 340 (81).

7,8-Dimethoxy-1,2-dimethyl-5*H*-chromeno[3,4-c]pyridin-5-one 456



454 **456**

A solution of **455** (0.568 g, 1.46 mmol) in *o*-DCB (15 mL) was placed in a sealed tube and heated to 220 °C for 16 h. The reaction mixture was cooled to room temperature and extracted with hydrochloric acid (2 M; 3 × 20 mL). The combined aqueous layers were concentrated *in vacuo* to afford the crude product as the hydrochloride salt. The residue was taken up in chloroform (25 mL), washed with sodium hydrogen carbonate

(25 mL), dried over $MgSO_4$ and concentrated in vacuo to afford the *title compound* as a pale orange solid (0.158 g, 38%); (Found: MH^+, 286.1068. $C_{16}H_{15}NO_4$ + H requires 286.1074); ν_{max} ($CHCl_3$)/cm^{-1} ; δ_H (400 MHz; $CDCl_3$) 9.30 (1 H, s, ArH), 7.97 (1 H, d, J = 9.2 Hz, ArH), 6.93 (1 H, d, J = 9.2 Hz, ArH), 4.00 (3 H, s, OMe), 3.99 (3 H, s, OMe), 2.75 (3 H, s, Me), 2.73 (3 H, s, Me); δ_C (100 MHz; $CDCl_3$) 164.0 (C), 160.4 (C), 155.0 (C), 149.6 (CH), 147.1 (C), 140.3 (C), 137.0 (C), 125.6 (C), 123.5 (CH), 114.4 (C), 112.1 (C), 107.7 (CH), 61.6 (OMe), 56.3 (OMe), 25.0 (Me), 19.2 (Me); *m/z* (ESI) 308 (MNa^+, 49%), 268 (MH^+, 100).

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